Transcript of June 20, 2001 Meeting

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HEALTH CARE FINANCING ADMINISTRATION
Medicare Coverage Advisory Committee
Meeting of the Drugs, Biologics
and Therapeutics Panel

June 20, 2001

Baltimore Convention Center
One West Pratt Street
Baltimore, Maryland

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Panelists

Chairperson
Thomas V. Holohan, MA, MD, FACP

Voting Members
Kathy J. Helzlsouer, MD, MHS
Robert C. Johnson, MS
Ronald P. Jordan, RPh

Mitchell Sugarman, MBA, MS

Temporary Voting Member
Emil P. Paganini, MD, FACP, FRCP
Temporary Non-Voting Member
Paul Metzger, MD

Industry Representative
Cathleen M. Dooley, MBA
Consumer Representative
Christine M. Grant, JD

HCFA Liaison
Sean R. Tunis, MD, MSc
Executive Secretary
Kimberly Long

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PANEL PROCEEDINGS

(The meeting was called to order at 8:35 a.m., Wednesday, June 20, 2001.)

MS. LONG: Good morning and welcome, panel chairperson, members and guests. I am Kimberly Long, Executive Secretary of the Drugs, Biologics and Therapeutics Panel of the Medicare Coverage Advisory Committee. The panel is here today to hear and discuss presentations regarding the use of levo-carnitine in end stage renal disease patients.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of impropriety. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests. To determine if any conflict existed, the Agency reviewed all financial interests reported by the panel participants. The Agency has determined that all members may participate in the matters before the panel today.

With respect to all other participants, we ask in the interest of fairness that all

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persons making statements or presentations disclose any current or previous financial involvement with any firm whose products or

services they may wish to comment on. This includes direct financial investment, consulting fees, and significant institutional support.

Also for the record, voting members present for today's panel meeting are Kathy Helzlsouer, Robert Johnson, Ronald Jordan, Mitchell Sugarman, Emil Paganini. Dr. Thomas Holohan will vote in the event of a tie. A quorum is present and no one has been recused because of conflicts of interest.

And now I would like to turn the meeting over to Dr. Sean Tunis and Chairman Dr. Thomas Holohan, who will ask the panel members to introduce themselves and disclose for the record any involvement with the topics to be presented.

DR. TUNIS: Thanks, Kimberly. Welcome again, panelists, and welcome to our guests and observers. We should have an interesting meeting today. The only additional housekeeping to do is just let you know that we are still operating under the rules of the, that the Executive Committee will review and ratify the

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recommendation made by this panel. The change in that, the change that is planned to take place October 1st is that the Executive Committee won't have a ratifying function in the future, but since this panel meeting is taking place still under our old charter, it is likely but not certain that the Executive Committee will also consider this issue and ratify whatever recommendations are made today.

We will, since some of you were asking, in terms of the specific questions that you will be addressing today, those will be presented by Dr. Klassen and Dr. John Whyte, so we will be getting into that part of the presentation.

All I would like to do now is turn it over to Dr. Holohan and have Dr. Holohan introduce himself and the rest of the panelists introduce themselves, and to state for the record whether they do have any conflicts that they need to

disclose.
DR. HOLOHAN: Thank you, Sean. I am Tom Holohan, I am the chair of the panel, and the chief of patient care services in the Veterans Health Administration in Washington D.C. I have no interest in this issue or this product one way or

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the other.
DR. JORDAN: I am Ron Jordan, HCaliber Consulting Corporation, no interests or conflicts with this product.
MR. SUGARMAN: I am Mitch Sugarman, director of medical technology assessment for Kaiser Permanente. No interests or conflicts.
COMMISSIONER GRANT: I am Commissioner Chris Grant, Commissioner of Health and Senior Services for New Jersey, and I have no interest or conflict in this product.
DR. METZGER: Paul Metzger, carrier medical director for DMERC Region C. No interests or conflicts.
DR. HELZLSOUER: I am Kathy Helzlsouer, a medical oncologist and professor of epidemiology at the Johns Hopkins School of Public Health and I have no interest or conflict in this product.
MS. DOOLEY: I'm Cathy Dooley, I'm the industry rep on this panel, a nonvoting member, and I have no conflicts.
DR. PAGANINI: Emil Paganini, section head of dialysis and extracorporeal therapy at the Cleveland Clinic.
MR. JOHNSON: I am Robert Johnson,

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assistant dean at the college of pharmacy, Northwestern University in Glendale, Arizona, and have no conflict of interest.
DR. TUNIS: For the next part of the meeting, we have invited, as we do for all our panel meetings, an independent expert to simply review the basic clinical and scientific background on the issue we are to discuss today

and for that purpose, we have invited Dr. Glenn Chertow to present on this background clinical information, and then we will move on through the agenda.

DR. HOLOHAN: Sean, I wanted to raise an issue. We had discussed earlier the possibility that time permitting, individual panelists could ask clarifying questions of any of the people presenting oral testimony. With Kimberly being the appropriate time keeper to keep us honest, I think we should make that opportunity available to anybody on to the penal.

DR. TUNIS: Hopefully there will be time for questions, both during the, or following the formal presentation and also as we get into the open panel deliberations, any panelist is invited to reinvite any member of the audience who

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has spoken either in the public comment period or any of the other people who have spoken, to direct questions to anyone in the audience at any point during the open deliberations, so there will be an additional opportunity to ask questions of the experts and guests.

DR. CHERTOW: Thank you, committee experts and guests. Thank you for inviting me. I will keep this very brief, but I will remain at the meeting for the day if you have any additional questions or issues.

I wanted to just raise a couple of points, if I can, just some reasons why I might be qualified to comment here. Thanks to Dr. Kopple, who was the chair of our work group, I was appointed vice chair of K/DOQI, a nutrition work group charged with reviewing and synthesizing information regarding levo-carnitine. I have board certification in internal medicine, nephrology and nutrition support. I serve as an associate editor to relevant nutrition journals, and practice as an academic nephrologist and do consider myself an advocate for persons with ESRD.

I have no financial relationship with

Sigma Tau, I receive no research funding for

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L-carnitine research. I'm on the full-time faculty of UCSF. I have served in an advisory capacity or received research funding from other companies, but not from any relevant to the presentations today.

Very briefly, L-carnitine is a water soluble substance, which is relevant in that dialysis removes water soluble substances, that facilitates transport of long chain fatty acids, which metabolizes fat into mitochondria, which are parts of the cell. The majority of L-carnitine is derived from dietary sources, principally dietary protein. Deficiency states which are clear, associated with acidosis in persons, usually children, with inborn errors of metabolism, for example, methylmalonic aciduria and other childhood diseases of acidosis.

But there are a variety of states of acquired L-carnitine deficiency, one of which will be addressed today, and one could become L-carnitine deficient by one of three mechanisms. Either there could be decreased L-carnitine intake; this might occur in malnutrition particularly among individuals with very low dietary protein intake and individuals undergoing

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severe dietary restrictions or those on perienteron nutrition who fail to have supplementation with carnitine.

There can be binding of L-carnitine, making it inactive to do its work in the metabolic machinery. The most common way that this is binded is with the anticonvulsant drug valproic acid or Depakote. This is another often forgotten acquired state of L-carnitine deficiency.

And then any form of increased L-carnitine clearance, which appears to occur in the setting of other anticonvulsant uses, particularly carubinose or Tegretol use and in

dialysis, because of the fact that the molecule is water soluble, as I mentioned earlier.

Reduction ratios of the three carnitine compounds are in excess of 50 percent with the usual dialysis prescriptions that are achieved.

There are a variety of proposed indications for levo-carnitine in end stage renal disease. They include among them asthenia, malaise, muscle weakness, intradialytic cramps and hypotension, cardiomyopathy, erythropoietin resistant anemia, and what I put in quotes, "quality of life."

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These indications are compelling, and not to suggest that HCFA doesn't have their interests in the patients, clearly they do, but there are cost implications that are relevant to HCFA as well. To the person with ESRD, asthenia, muscle weakness and intradialytic symptoms are extremely important, they contribute greatly to the overall sense of well being or lack thereof, and it's worth noting that levels of physical activity even for healthy persons with ESRD are markedly reduced. We showed in a recent publication that even for a group of healthy people on dialysis, that their overall level of physical activity measured by a three-dimensional accelerometer was similar to the levels of physical activity achieved by persons with multiple sclerosis.

So these kind of very subtle difficult to measure symptoms are considerably important to the people with ESRD. To the HCFA, I gather you all have changed your name now, but cardiomyopathy is relevant in that hospitalization for congestive heart failure is extremely common, it occurs in more than 10 percent of patients on dialysis per year, and it's a very costly complication, and

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with coverage for erythropoietin, it would be in the interests of a coverage agency to consider

whether this agent was effective in controlling erythropoietin resistance.

Very briefly, I will describe for you the process that we undertook with the K/DOQI work group. I have to say, I was charged by Dr. Kopple in part because I'm objective and trained in epidemiology, and also in part because I had had no prior research experience with the compound, so I could as the subleader of this segment of the clinical practice guideline development be as objective as possible.

We reviewed the levo-carnitine studies based on evidence criteria which we actually modified, compared with the evidence criteria for the rest of the guideline, because of the overall paucity of randomized clinical trials and other large studies. The work group is a ten-person group, chaired by Dr. Kopple, comprised of seven MDs and three very experienced registered dieticians, and the group was coordinated -- the literature review and process was coordinated by some excellent Rand scientists.

As in all evidence based guideline

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development projects, randomized clinical trials were emphasized. The following studies which were included in your packet for today, the Brass, Kletzmayer, Semeniuk and Thomas studies were not reviewed due to the timing of publication since we had to limit our review through I believe mid-1998.

And our general summary of the work group findings as you see them published in the American Journal of Kidney Disease was that the totality of evidence was in unimpressive, but there was a known risk of functional deficiency and potential consequences and a favorable side effect profile. So the work group concluded that a therapeutic trial would be reasonable if other causes of symptoms, for instance, inadequate dialysis or pharmacologic therapy for heart disease had not been identified with thorough

investigation.
And obviously as the development of a clinical practice guideline, these recommendations were not intended to direct coverage decisions. And with that, I'll stop and be available, should you have any other questions.
DR. TUNIS: Go ahead, Kathy.

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DR. HELZLSOUER: I wonder if you could tell me, explain to me what K/DOQI is, and the panel, and give me a little bit background on that.
DR. CHERTOW: Sure. K/DOQI is the evolution of what used to be called NKF DOQI or just DOQI, which is the Dialysis Outcomes Quality Initiative. This was a series of clinical practice guidelines which were developed and led by the National Kidney Foundation. The name has been changed from Dialysis Outcomes Quality Initiative to Kidney Disease Outcomes Quality Initiative, perhaps for the same reasons that HCFA is changing their name.
But the National Kidney Foundation felt that clinical practice guidelines could extend beyond dialysis into earlier stages of kidney disease, so they simply changed the name. But this is a process which has led to, thus far, the publication of five clinical practice guidelines, one for adequacy of hemodialysis, one for adequacy of peritoneal dialysis, one for management of anemia, and one for management of the dialysis vascular axis. And ours, which Dr. Kopple led, was the guideline for nutrition in chronic renal

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failure.
DR. HELZLSOUER: The other question I had, maybe you can educate me a little bit about carnitine deficiency in general, so for even other people that have it, what are the symptoms and if you replaced that, what's the evidence or did you look at that evidence at all?

DR. CHERTOW: Well, many of those papers were included in the packet. Among individuals with end stage renal disease. I'm not a pediatric metabolist, but some of these pediatric states of carnitine deficiency are associated with acidosis, very poor growth, and other complications. There are some states of carnitine deficiency which lead to rhabdomyolysis or muscle breakdown, because of carnitine deficiency in the muscle. And in adults, the complications can include acidosis, but metabolically more commonly include hyperammonemia or high levels of blood ammonia because of the role carnitine plays in the urea cycle, and typically muscle weakness, muscle symptoms.

DR. HELZLSOUER: Thank you.

DR. HOLOHAN: Did you address the route of administration in reviewing the data?

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DR. CHERTOW: We felt that the evidence overall, the number of very high quality studies that have been conducted using either oral or intravenous levo-carnitine were very small, and so we specifically didn't address the intravenous versus oral administration issue in that review. It was hard enough to amass studies that were really high quality, as judged not only by the work group but by the Rand scientists.

DR. HOLOHAN: Thank you.

DR. PAGANINI: Just a quick one. The DOQI group is not just one society, but actually the getting together of all national renal societies that have participated in developing these guidelines, so it is in the true sense, the development of true practice guidelines, across not only single society expertise, but multiple society expertise, not only across one subspecialty, but multiple subspecialties, to also include patients and patient advocacies, et cetera, industry.

So these guidelines have in fact been quite vigorously developed and have been used by

HCFA and others as a basis for a lot of decisions internally as well as externally. For example the

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(inaudible) program looks through its networks to look for quality maintenance and the network system will in fact use these guidelines to establish methods of evaluating th efficacy of dialysis, et cetera, so the guidelines carry with them some strong evidence based and rigorous reviews for development of guidelines.

DR. CHERTOW: And based on, the first four have been updated, and the intention was that we would have periodic updates with accumulation of new information.

DR. METZGER: That last update was June 2000.

DR. CHERTOW: Yes, but the nutrition practice guidelines were not updated along with the other four, they had come after. Ours were published in 1999 or in 2000?

DR. KOPPLE: June 2000.

DR. TUNIS: Dr. Chertow, this is again related to the DOQI guide lanes. Is it possible to describe at all the sort of standard of evidence, if you will, that was used in terms of you know, were recommendations based on both the expert opinion as well as the scientific articles, or basically if there weren't explicit high

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quality kinds of articles, was no recommendation made, or where did DOQI sort of fall in?

DR. CHERTOW: In the nutrition practice guidelines, most of the guidelines were based on a combination of evidence and opinion. There were very few in which the evidence was so strong that some expert opinion wasn't required.

DR. TUNIS: And was there actually a formal rating system for that, did you give them A, B and C depending on that, or how did it work?

DR. CHERTOW: Well, that was coordinated principally by a scientist at Rand,

Paul Chakel, who had done that very early in the process, where we basically rated all of the articles as either evidence by a very rigorous series of criteria, or opinion, and actually those articles which were not deemed of sufficient quality to be considered evidence by their definition were not included in the review, almost as if evidence ignored by the panel, although it could certainly be incorporated in the opinion components of the guidelines, but not, but they wouldn't be included if the guideline as designated as evidence, it would only be based on the few studies that had been considered evidence

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by the group. And that was done formally and quite early in the process.

DR. TUNIS: And so within that range again, where did the recommendations related to carnitine supplementation, where did those fall within that spectrum?

DR. CHERTOW: They were based on a combination of evidence and opinion. But again, because the quality of the evidence was less in that domain than in some of the other areas that we studied, there was probably more opinion and less evidence, though it was clearly a combination of the two. Would you agree with that, Dr. Kopple?

MR. SUGARMAN: I'm sorry to keep going over the same issue, but is it fair to say then that the way you reconciled an evidence based process with the lack of evidence was by supplementing opinion?

DR. CHERTOW: Exactly.

MR. SUGARMAN: Thank you.

DR. HOLOHAN: I should take the opportunity to do some marketing Dr. Chakel, whom Dr. Chertow referred to, as a researcher full time at the West Los Angeles Veterans Administration

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Medical Center.

DR. TUNIS: The only thing I want to mention about DOQI and I am not an expert on this, but could somebody describe it, it's my understanding that the funding for DOQI came entirely from AMGEN, or was it combined AMGEN and the National Kidney Foundation or what was the sort of sponsorship and -- but I know it was contracted then to an independent consulting firm or something, but can you just describe that arrangement at all?

DR. CHERTOW: I could, but since Dr. Kopple is the past president of the National Kidney Foundation, he could probably comment on it more knowledgeably than I.

DR. TUNIS: Is that all right?

DR. HOLOHAN: Sure.

DR. KOPPLE: My name is Joel D. Kopple, K-O-P-P-L-E, and you're almost correct. The first four guidelines and a number of the ones that are currently in process are funded not entirely but largely by AMGEN. The nutrition, chronic renal failure guidelines in fact were funded not entirely, but largely by Sigma Tau.

Can I make one other comment to this

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young woman about, in answer to your question? Carnitine is essential for life. Children with inborn errors of carnitine synthesis usually die at the age of eight, nine, ten, 11 years old. Their death is usually due either to intractable congestive heart failure, they develop a massive dilated cardioneuropathy, or to fatal arrhythmias. In these children, treatment with carnitine is life saving, completely; if you get them in time, the treatment essentially saves their life, they may be able to live a normal life style.

DR. HELZLSOUER: What about the other area? You mentioned the valproic acids. Are there other ones that might be a little more assimilated in inborn errors of metabolism so the situation we're dealing with if there is a deficiency here in what has, what's known about

that?

DR. KOPPLE: I'm going to have to take the same defense that Dr. Chertow did, I'm not a pediatrician. My reading of that literature is in fact that it will reduce the severity of the lactic acid or the other acidemias, organic acidemias that occur. The result is not as dramatic, in my understanding, as it is if in fact

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carnitine was not synthesized.

DR. HELZLSOUER: Thank you.

DR. TUNIS: Thank you. Any other questions for Dr. Chertow? Again, he will be available later in the day.

I believe the next item on the agenda is the FDA presentation. The FDA staff person wasn't able to attend in person and they did within the last few minutes, they were finally able to submit to us by fax a statement which I'm going to read to you all and which has just been circulated to the committee. We will make copies of this available and put it on the table outside for all members of the public, so this is the FDA statement:

The memo is from Dr. David G. Orloff, Director, Division of Metabolic and Endocrine Drug Products, it's a memo to Dr. John Whyte at HCFA. The subject: Brief summary of basis of approval of Carnitor for the prevention and treatment of carnitine deficiency associated with end stage renal disease in patients undergoing chronic hemodialysis.

Brief rationale for the approval: Patients with ESRD can develop secondary carnitine

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deficiency as a result of poor nutrition, inadequate endogenous biosynthesis, and through dialytic losses. Clinical manifestations of carnitine deficiency generally do not ensue until levels fall to less than 20 percent of normal. Under current standard of car, which includes

carnitine supplementation, hemodialysis patients do not develop clinically manifest carnitine deficiency. It would, furthermore, be unethical to subject patients to the risks and discomforts of frank carnitine deficiency in a study designed to assess the clinical benefit of carnitine supplementation. There is ample evidence that carnitine is an essential metabolic intermediate and that carnitine deficiency, regardless of cause, can be a serious and life threatening condition. In light of the safety of carnitine, an overall salutary effect of carnitine supplementation in ESRD can be inferred from data showing that carnitine levels are maintained or increased in these patients who are subject to carnitine depletion and ultimately, therefore, to clinical carnitine deficiency.

Review Summary: In response to a letter from the Agency in 1988 denying approval

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for the proposed indication in ESRD patients because of lack of evidence of clinical benefit, the sponsor submitted new data from two placebo controlled trials of the safety and efficacy of thrice weekly Carnitor injections after dialysis. These data addressed the effect of the treatment on serum carnitine levels as well as on biochemical parameters such as predialysis BUN, creatinine, phosphorus, on hematocrit, and on the incidence of hypotensive episodes in association with dialysis.

The data addressing the effect of carnitine at three different doses administered three times weekly after dialysis show that the therapy readily increases in predialysis carnitine levels. There were no safety issues raised in review.

The FDA clinical team leader's review notes the following: "The data clearly support the efficacy of intravenous levo-carnitine in maintaining or increasing carnitine serum levels in ESRD patients on dialysis; however, they do not

support improvements in clinical status or exercise tolerance, nor do they provide convincing evidence for decreases in BUN, creatinine,

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phosphorus, for increases in hematocrit, and for decreases in hypotensive episodes. Levo-carnitine supplementation after dialysis is a safe and effective means by which to treat or prevent clinical carnitine deficiency in ESRD."

And that's the end of that memo which you all have a copy of. And again, there will be copies of this made available for everyone in the audience. And given that I won't be able to take questions on that, we will move on to the HCFA presentation.

DR. WHYTE: Good morning, I am John Whyte, and over the next 20 minutes Dr. Klassen and I are going to do the HCFA presentation, and as you heard from Dr. Chertow, we do have a new name, so it is a misnomer and so I guess I really should call it the CMS presentation, for the Center for Medicare and Medicaid Services. Why it's not CMMS, I don't know, but it's CMS, for the Center for Medicare and Medicaid Services.

Now, you have heard from Dr. Chertow this morning about the clinical background of carnitine and carnitine deficiency, and Dr. Tunis has read a letter from the FDA, and you have in the packets that were sent to you prior to this

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meeting the FDA approval of parenteral levo-carnitine. I am not going to discuss the clinical background or the FDA process. It is important to our process and the point that I want to make is that FDA approval is a prerequisite but it is not a guarantee for coverage.

Now I'm going to talk a little bit about the reasons why we referred it to the Medicare Coverage Advisory Committee, and this issue first came to our attention several months ago when different carriers had different policies

on carnitine, and you have some copies of the local medical review policies which are the policies of the carriers, in the packet that was sent to you prior to this meeting.

When we started to look into this issue, what we found is that different groups had very different opinions on the same data. So Dr. Tunis, myself and others felt that it was important to have an open meeting where all participants could present their interpretation of the data, and we thought that would best be done with a systematic literature review, which we are going to go over, and then everyone would have an opportunity to present their opinions and everyone

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else would have opportunities to present their opinions on those people's opinions, so hopefully we will be able to do that today.

I talked about it all starts with a systematic literature review, and when you first start about doing this review, you have to think, what are the questions that we're trying to ask. So the questions that we determined were important relating to carnitine ESRD patients is first, what is the evidence that ESRD patients on hemodialysis develop carnitine deficiency?

We're going to stipulate up front that ESRD patients can develop carnitine deficiency, so we're not going to discuss at this meeting today whether or not ESRD patients develop carnitine deficiency but for the sake of discussion, let's assume that they can.

The second question is, what is the evidence that L-carnitine deficiency is involved in the pathogenesis of disease.

Third, what's the evidence that the administration of L-carnitine to ESRD patients improves clinical outcomes.

And then finally, what is the evidence that one particular route of administration or

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dosage regimen is superior.

So those were the questions that we started off when we wanted to do our systematic literature review. So in terms of our search strategy we used the words carnitine, kidney failure, chronic or renal dialysis, or dialysis.

What we found were 186 articles. 44 were excluded on the first pass, either because they were non-English, they were case reports, they didn't deal with human subjects, they dealt with acute renal failure, and we were primarily interested in chronic renal failure. Of the remaining 142 studies, there were 16 randomized clinical trials, 51 prospective clinical trials, 30 case controls or cohort studies, 22 reviews or editorials, and 23 letters to the editors.

So from this 142 articles, we had to develop some inclusion criteria and apply the inclusion criteria to these articles. These inclusion criteria were that they had to deal, the studies -- first of all they had to be clinical trials, but secondly, they had to deal with human ESRD subjects, they had to have a minimum of 10 subjects in total, had to be published after 1980, had to have clinically relevant outcome measures.

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And by these clinically relevant outcome measures, we meant things such as cardiac function, lipid profile, hematology issues such as anemia or issues relating to coagulation. Had to relate to some metabolic outcome, they had to relate to muscle and exercise strength, or there had to be some quality of life issue or intra or interdialytic symptoms.

So after applying these inclusion criteria, we ended up with 36 articles, including all the RCTs that we started off with from the beginning, which were 16, 19 prospective clinical trials, and one case series.

At this point I'm going to turn to Dr. Preston Klassen, who is a nephrologist working with us in coverage, who will discuss the

literature review.

DR. KLASSEN: Thank you, Dr. White. My name is Preston Klassen. First I will make some comments about the 36 studies reviewed, and then summarize study date according to five categories of clinical condition to outcomes.

The overall subject population from the 36 studies is approximately 1,100 subjects, which is a bit less than the summation of subjects

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across all the articles because there are several pairs of articles reporting different outcomes from the same study population. 24 studies investigated intravenous administration of carnitine, 12 studies investigate oral administration, and 4 looked at placing carnitine in the dialysate solution that equilibrates with a patient's plasma during the dialysis treatment procedures. These numbers add up to more than 36 because several studies looked at multiple routes of carnitine administration.

I will also note that the vast majority of the studies examined L-carnitine. There were a small number of investigations of DL-carnitine prior to and in the early 1980s. L-carnitine was reported to cause a myosteoma-like neuromuscular syndrome that appeared to be dose dependent; however, that formulation is no longer used and similar symptoms have not been reported with L-carnitine.

In general, the number of subjects in the studies was small. In fact, only 9 of the 36 studies enrolled more than 30 subjects. The study duration varied from as little as four weeks to greater than one year, with a mean follow-up of

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23.3 weeks. A majority of these studies did utilize double blinded methodology when a placebo control group was present. However, the statistical analysis of active therapy and control groups in a number of the studies utilized within

group comparisons between baseline and end of therapy parameters instead of between group comparisons. This type of within group analysis is less rigorous than between group comparisons and might affect the significance of the overall study outcome in that it does not account for potential placebo effects, and we'll take a look at an example of that as we review the study data.

We found that the reviewed studies reported on a wide variety of outcome measures, primarily putative surrogate measures. This variety of outcomes makes it difficult to talk about aggregate results across all the articles. We therefore grouped the studies into five general categories which were similar to categories used in the K/DOQI literature review, and those categories are: Anemia; this is primarily reporting on changes in hemoglobin, hematocrit and recominant human erythropoietin requirements. Exercise capacity; this category includes

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primarily objective measurements of exercise muscle strength and changes in muscle fiber morphology by histologic examination of biopsy tissue. Cardiac function, which basically includes the presence of arrhythmia and quantification of ejection fraction. The next group is intra and interdialytic complications or symptoms; this primarily includes interdialytic hypotension, muscle cramps, fatigue, asthenia, as measures of general well being or quality of life.

Now, intradialytic hypotension has been categorized under the cardiac dysfunction category in some reviews, and cardiac dysfunction can cause vascular instability during dialysis. However, other noncardiac etiologies for hypotension do exist, and that includes excessive food removal during the dialysis procedure. In the absence of a specific examination of cardiac function, we consider hypotension under this symptom or complication category.

At the final category is lipid

metabolism.

I will now ask the panel to follow along in the handout that we presented as most of the summary tables may be difficult to read on the

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slides. The first category is the effect of carnitine on anemia parameters. 11 studies were reviewed. In five of the articles anemia was a primary focus, in the others it was a secondary outcome. All but two included less than 30 patients. Eight studies involved IV carnitine, two involved oral carnitine, and one delivered carnitine via dialysate.

Since iron status is an important factor in the management of anemia in end stage renal disease patients, we looked at whether each study incorporated measures of iron status. Six did, including one study which used active iron therapy in all subjects, and five did not.

Hemoglobin was reported in six of the studies and not reported in five. Of the six that did report on hemoglobin, five showed no change after carnitine therapy and one showed a significant increase.

Of the seven studies reporting on hematocrit, three reported an increase in hematocrit after carnitine therapy, two reported no change in the active carnitine group but a decreased hematocrit in the placebo control group, and three showed no change with either no control

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group or no change in the control group.

This summary on the table does include a subgroup analysis which done in the paper by Caruso. In Caruso's study, 31 patients were randomized to six months by their IV carnitine therapy, one gram after each dialysis treatment, or placebo. After six months, both groups were followed for three months without any intervention, no carnitine, no placebo, for a total of nine months. Overall, there was no

statistical change in hematocrit in either group at phase two or the end of the six-month intervention, or at phase three, the end of the follow-up. However, when a subgroup analysis was performed on subjects older than 65, which was the majority of the study population, comprising 22 patients, the placebo group had a lower hematocrit at the end of the follow-up at month nine, while the carnitine therapy group had no significant change.

Turning to recomitant human erythropoietin requirements, of the 11 studies, five reported on erythropoietin requirements. Of these, the study by Matsumura was a correlation between baseline carnitine levels and

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erythropoietin requirements without any carnitine supplement intervention. In this case series, erythropoietin requirements and indices of red cell hemolysis both correlated inversely with total and free plasma carnitine levels.

Of the four interventional trials, three showed a decrease in erythropoietin requirements after carnitine therapy, one showed no change in the carnitine group, but an increase in EPO requirements in the control group, and one showed no change overall.

This summary again includes that Caruso subgroup analysis. Overall, Caruso showed no change in the carnitine treated group, but an increase in EPO needs for the placebo group at the end of the follow-up, at nine months. In the subgroup analysis, so just patients over the age of 65, patients in the carnitine group did have lower EPO requirements after six months, and that requirement rose again significantly after three months of receiving nothing.

I will also point out two other studies showing a decrease in erythropoietin measurements. In Kletzmayer's randomized control trial of 40 patients over eight months, the carnitine group

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had a nonsignificant decrease in erythropoietin requirements. Another measure that they used, the erythropoietin resistance index, which is a calculated measure, basically, the weekly dose of EPO per a gram of hemoglobin that's maintained by that dose, so it's a calculated index measure, that was calculated and a significant decline in its resistance index was seen in the carnitine treated group. They also pointed out that a positive effect of carnitine therapy could be seen in eight of 19 subjects, labeling these eight as responders and the others as nonresponders.

Labonia randomized 24 patients in a six-month trial. Subjects receiving carnitine had a 38 percent reduction in EPO dose, measured in terms of units per kilogram per week. Control subjects had no reduction. The authors note that this reduction in the carnitine group was powered by seven of 13 patients who responded, compared to six who did not respond, again, a finding of a differential effect of carnitine therapy similar to Kletzmayer.

The next slide summarizes the effects of carnitine on exercise, muscle strength and muscle morphology. These studies represent a

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variety of outcome measures; for example, muscle strength is analyzed in five articles, two using objective measures of torque or isometric force, one using objective EMG measures, and two using patient self assessment scores. The outcome measures across all studies are summarized in the second table on this page.

One study by Ahmad examined body anthropometric measures and found a significant increase in mid-arm muscle mass in the carnitine control group with no change in the placebo group.

Two studies examined maximal oxygen consumption, the studies by Ahmad and Brass. Ahmad showed an increase in maximal VO-2 in the carnitine group, Brass did not show a difference

in the primary analysis. They then performed a secondary analysis using different regression techniques, and did show a smaller decline in the max VO-2 in the carnitine group compared to the placebo. Ahmad also looked at exercise time and found no significant differences.

As I mentioned, five studies looked at muscle strength. Two were positive and three were negative. The two positive studies used objective measures, isometric force and EMG activity; the

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negative studies did include two subjective assessment scales and one objective measure of torque force. Muscle and fiber morphology was measured in three studies; two were positive, showing either an increase in fiber diameter or a decrease in fiber atrophy scores, and one was negative, showing no change.

The next clinical category is inter and intradialytic complications and patient well being, and again, this is a group of studies with heterogeneous outcome measures. Generally, these were intradialytic hypotension, muscle cramps, fatigue, asthenia, and quality of life measurements. Although the outcomes are varied, five studies had a positive effect or improvement in at least one outcome after carnitine therapy, three studies had no evidence of effect, one study had both positive early and negative late effects. Of the five IV studies, two were positive and three were negative. Of the oral studies, three were positive and one had both positive and negative effects.

The study with both positive and negative effects was authored by Sloan, involved a large number of subjects, 101, in what was really

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two studies, a compilation of two studies. One was a randomized control trial and the other was a double-blind crossover trial. Quality of life was measured by a standard SF-36 tool, and in both the

randomized control trial and in a combination of the two trials, it appeared that the intervention, oral carnitine, had initial positive effect on physical function and general health but that after a four to six-month period, there was a greater decline in the carnitine treated group compared to the subjects on placebo.

I would like to point out the study by Brass as an example of within group and between group comparisons. This is also a study of a large number of subjects, 183, and it involves two separate trials of 24 weeks duration, one a randomized control trial comparing 20 milligrams per kilogram IV and the other more of a dose finding study, or dose application study, randomizing patients at 10, 20 and 40 milligrams per kilogram, or placebo. Quality of life was measured by the KDQ, a kidney specific validated quality of life tool, and the difference between total quality of life scores at baseline and 24 weeks is shown to be .44, the mean difference in

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score, for the carnitine treated group, and .29 for the placebo treated patients. So carnitine treated patients appear to have a greater improvement. That's the within group comparison, baseline to end of study for each group.

But between group comparison essentially takes into account the changes in the placebo group when evaluating the change in the carnitine group, and this difference comes out to be not statistically significant can.

We reviewed four studies of cardiac function and carnitine. As a secondary outcome, Ahmad's randomized control trial of 82 subjects examined arrhythmias during dialysis. Overall, there was no decrease in arrhythmias in the carnitine group compared to the placebo group. Both groups did have few subjects with arrhythmias at baseline and the study may have been underpowered to detect a difference.

Suzuki also looked at arrhythmias,

specifically in eight subjects with premature beats, both ventricular and supraventricular, during dialysis. All subjects took oral carnitine for eight weeks and there was no control group for the carnitine administration phase. Suzuki showed

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a significant reduction in the number of premature beats both at four and eight weeks compared to the baseline values for that group.

Ejection fraction was measured by two studies, by Fagher and Van Es. Fagher performed a six-week randomized control trial in 28 subjects using echocardiography to evaluate ejection fraction and other cardiac parameters. Using between group statistical comparisons, there was no difference in any parameter. This study may have been limited in its ability to detect any difference by the short duration of the trial and the fact that overall the patients had normal ejection fractions to begin with.

Van Es looked at 16 patients in a prospective clinical trial, split into symptomatic and asymptomatic patients depending on whether or not they were experiencing hypotensive episodes during dialysis. Each subject received IV carnitine for three months and then had ejection fractions measured first at baseline and then at three months by gated pool nuclear imaging. Only 13 patients had post-treatment examinations. Over the 13 patients as a group, there was an increase in ejection fraction from 24, I'm sorry, from 42.4

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to 48.6. This change was driven entirely by the seven symptomatic patients who started with lower ejection fractions to begin with, 30 compared to 52, and in the symptomatic group that increased by 37 percent compared to 9 percent in the asymptomatic group.

The final group of studies is concerned with carnitine and lipid parameters and in the interest of time I am not going to discuss the

specific individual studies, but I will summarize the 17 studies reviewed. The outcomes were triglycerides, cholesterol, HDL. LDL was reported actually in only a few of the studies. Ten studies used IV carnitine, six used oral, and two used dialysate delivery. There were six randomized control trials and 11 prospective clinical trials. Triglycerides showed no change in nine studies, a decrease in six studies, and an increase in one study. HDL showed no change in 11 studies and an increase in three. Cholesterol showed no change in all 17 studies.

Overall, the majority of results revealed no significant changes in lipid parameters. There were no studies that directly compared carnitine therapy to conventional lipid

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lowering therapy.

Dr. Chertow summarized at the beginning the review and conclusions of K/DOQI with respect to carnitine and you have a copy of that in your packet. In all of the clinical categories that we have discussed, with the exception of lipids, our list of articles differed from what K/DOQI found by only one or two. There was a greater variation in the lipid articles; however, the general data summary was similar to the data summary found in K/DOQI.

At this point I am going to turn to Dr. Whyte for discussion on the questions that are now before the panel. Thank you very much.

DR. WHYTE: We'll come back to questions right afterwards. The questions relating to the panel, you have a copy in front of you and copies of the questions are also available on the table outside this room. These are the questions that we're going to ask you to vote on at the end of the meeting, and we ask that the speakers that come after us try to address these questions.

And essentially there's two questions, although as you will see on your paper there are

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some subquestions. The first question will be, is there adequate evidence that the administration of intravenous L-carnitine is effective as a therapy to improve clinical conditions or outcomes in patients with ESRD on hemodialysis?

The second part of that question will be, is there adequate evidence that the administration of oral L-carnitine is effective as a therapy to improve clinical conditions or outcomes in patients with ESRD on hemodialysis?

And we ask when you look at the clinical outcomes that you consider anemia, disorders of lipid metabolism, cardiac dysfunction, disorders of muscle strength, physical functioning or exercise capacity, and inter-intradialytic symptoms. And you can either look at that in the aggregate or you can decide to vote on those individually; we certainly defer to the panel to decide how you want to vote on that, again, whether in the aggregate or on each clinical condition.

So you first vote on intravenous and then you will vote on oral L-carnitine.

The second question will be, is there adequate evidence that the route of

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administration, whether intravenous, oral or the dialysis fluid, is an important factor in the clinical effectiveness or safety of L-carnitine therapy in patients with ESRD on hemodialysis?

And if you answer yes to that question, then we ask you to comment on which route of administration is preferred in the clinical care of these patients.

Also, on your handout, you have comments, which is our standard language about considering adequacy of study design, the consistent of results, and applicability beyond the research setting as you answer these questions.

And at this point in time, if the chair or other members of the panel have any questions for Dr. Klassen or myself, we would be happy to answer them.

DR. METZGER: I have a few, or two. The one on the lipids, my own analysis of these studies, it seems like there were an equal number of negative and positive studies for IV and PO, oral, which I don't know if you mentioned that.

DR. KLASSEN: I didn't comment specifically on the IV versus oral.

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DR. METZGER: Okay. And in fact in one study, the oral actually had a positive effect where the IV had a negative effect, or no difference.

The other question I had just reflects my own ignorance, I didn't have time to research this, but the Spagnoli study mentioned how the diameter of the type one fibers decreased and they referred to that as hypertrophy, and I could not understand that.

DR. KLASSEN: That's an interesting study. It's actually a carnitine withdrawal study because all the patients were receiving carnitine therapy for at least one year. They then had a withdrawal of carnitine, and I believe that was a four-month period of time, and then carnitine was initiated back in the dialysate this time, again for a four-month period of time. They did muscle biopsies at the start of the study, which was really the end of at least a year of therapy, so they never had baseline biopsies, so start of the study, the end of one year of carnitine therapy, again after four months of no therapy, and then again after four months of carnitine in the dialysate. And for the purpose of the study,

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there was really no difference between the second and the third biopsies, if I'm recalling that correctly.

So, type one muscle fibers are the fibers that exhibit primarily oxidated metabolism and would be expected to be affected by changes in carnitine, which affects (inaudible) fatty acids. So what they found was a decrease between when they were, had carnitine and then had a withdrawal or dialysate, a decrease in diameter of type one and if I recall correctly, a decrease in the hypertrophy score, which is just another reflection, and we can go over that at a break.

DR. METZGER: Sure. I may have misread it.

DR. KLASSEN: Without having it in front of me, my recollection of the data was that they were not disparate.

DR. HELZLSOUER: I have a question just on your terminology. You refer to prospective trials. Are you really meaning that they are uncontrolled because trials are prospective, so do you mean uncontrolled, no placebo, or are you referring to different designs?

DR. KLASSEN: That's a very good

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question and that term really encompasses a number of study types but they all include some interventional aspect that is not a randomized control trial. So, it may be an intervention on a group of patients with no control group or it may be an intervention on a group of patients that had a nonrandomized placebo control group.

DR. HELZLSOUER: Because my counts seem to have more randomized trials and I didn't know if you were including crossover designs in the prospective because they were still randomized, they were just crossover design, a different design.

DR. KLASSEN: For the purposes of our analysis, if a study said we randomized patients to two groups, group one started carnitine therapy for two months and then placebo for two months, the other group started placebo for two months and then carnitine for two months, the opposite, we

didn't consider that a randomized control trial because the two studies, the two groups were never directly compared to one another. We considered that to be prospective clinical, double blind placebo crossover trials, that's what we used.

DR. HELZLSOUER: You have to look at

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the terminology, because is puts it at a different level and I don't know if it necessarily should be that way, because there are recognized crossover designs.

DR. WHYTE: Sure. And we tried to specify that in your literature review that was sent to you prior to the meeting. We specified whether they were crossover designs, recognizing your point that some people might categorize those studies differently.

DR. HOLOHAN: Just one comment on the issue of randomization. I don't know how critical this is to you, but I only found one study that described the method they used to randomize. A lot of the studies said patients were randomized into two groups, but they didn't say how they did it, they didn't say whether they did it by day of the week or odd-evens. Only one study and that was Sloan's, actually described the mechanism for randomization.

DR. TUNIS: The only question I have, in the questions to the panel, obviously there is some focus on the issue of route of administration, and I don't know if in your sort of summary of evidence, did you at all try to look

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at any correlation between positive or negative studies in the route of administration, or is that just to be looked at kind of one study at a time?

DR. KLASSEN: Because of the difference, it's hard enough to look in the aggregate without considering dose of administration. Within the specific groups, when possible, we tried to at least report, you know,

which studies of IV had an effect, which studies PO had an effect, but it is a difficult issue to tackle in the aggregate. We did not specifically make a large section in the review about that.

DR. METZGER: I guess in my naivete I did a spreadsheet like that and it looked like, on the IV effects, if you do a spreadsheet with your parameters you're measuring versus IV versus PO, there are actually proportionately more positive studies with PO administration than with IV. IV had more negative or no difference, versus positive difference, for what that's worth.

DR. TUNIS: So we are now moving on to the scheduled public comments and the first scheduled presenter, C. Kenneth Merhling, from Sigma Tau Pharmaceuticals.

MR. MEHRLING: You see Brian

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Schreiber's presentation. I have a few comments I'd like to make first, so don't be confused that I'm going to talk off of his slides.

Good morning. My name is Ken Mehrling and I am the chief operating officer for Sigma Tau Pharmaceuticals in the United States and Canada and we are the makers of Carnitor injection, which is the topic of this Medicare Coverage Advisory Committee meeting. I would like to thank all of you for the time you have taken to review the material on this matter.

Sigma Tau has worked about ten years to develop the data and satisfy all the requirements that are necessary to obtain approval from the FDA in 1999 to market Carnitor injection for ESRD patients with carnitine deficiency. As will be described later, the approval was based and as you heard from Dr. Orloff, it was based on the FDA's careful assessment that the product was safe and effective for this indication.

It's also important to point out that Sigma Tau is the largest manufacturer and distributor of prescription levo-carnitine in the world. We have both the oral and intravenous

formulations on the market worldwide. In the

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United States we have submitted a request to the FDA to add a precaution to our package inserts for both Carnitor tablets and oral solution, and this precaution recommends against the use of the oral formulations in the ESRD patients, due to unknown safety concerns. These concerns will be discussed in subsequent presentations.

And we welcome the review by this panel, because we hope that it will help clarify the important role that Carnitor injection can play in the treatment of ESRD patients with carnitine deficiency. This review is crucial for our company and the patients it serves, and as a result, Sigma Tau Pharmaceuticals has provided financial assistance to various physician experts, FDA experts, patients and consumer advocates so that they could easily come to this meeting and testify.

I would like now to introduce Dr. Brian Schreiber, who is currently president of Fox Valley Nephrology in Appleton, Wisconsin, a practicing nephrologist who routinely treats ESRD patients. And I don't want to waste our limited time reading his credentials which are contained in the handouts, but suffice it to say that

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Dr. Schreiber has significant personal experience with use of Carnitor injection, in addition to an in-depth knowledge of both carnitine deficiency and its treatment. He has also consulted with us in preparing the materials that we submitted to you, and I would like to just turn that over, the remainder of our time to Dr. Brian Schreiber. Thank you.

DR. SCHREIBER: Thank you very much. Thank you for allowing me to address you today. As Mr. Mehrling said, I am primarily a clinical nephrologist in Wisconsin. We take care of the renal failure patients for a fairly large area in

Wisconsin. My interest in carnitine derives from what I observed clinically; because of what I observed clinically I developed an academic interest, and I have taught, lectured, published and done research with carnitine.

What I want to talk about today is from, however, the perspective of the clinician. In a sense, Dr. Klassen did an excellent job in reviewing the aggregate literature, and in the short period of time I have, I can't go over what he did. What I wanted to do, however, is look at that from a clinical perspective, because this

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panel has eminent experts in the statistical analysis of studies. However, every study, the conclusion of the study depends on the statistical aspects and the clinical aspects. And since my expertise is clinical I wanted to look at some of the clinical aspects of these studies that contribute to their findings.

I will talk briefly about clinical correlations and carnitine levels since these questions have been asked, mostly about medical evidence of efficacy based upon clinical differences in the study. We will try to glean from these clinical differences some general principles that may allow us to optimize the benefit from the use of carnitine in dialysis patients, speaking somewhat about oral versus IV as one of the important clinical differences, and if we have time, I would like to share with you algorithms that have been presented at the National Kidney Foundation national meetings and published that we have used in our dialysis units for several years now that have allowed us, I think, a responsible and reasonable and efficacious use of IV carnitine.

People have raised the issue of plasma

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levels and as a nephrologist I do feel that it is necessary to point out that these plasma levels,

all of which are quite low, represent maximum levels in the dialysis patients. These are the levels right before dialysis. Now we know for example, when we monitor potassium in our patients, potassium is a toxic, it is toxic to dialysis patients, we always get the highest level they're going to have, which is right before dialysis. We know that in the intradialytic period that level is quite a bit lower and we know that immediately after dialysis it's even lower. And the same has been shown with carnitine, that the post-dialysis levels of carnitine are extremely low, and actually below the 20 percent that you heard about, which is a threshold for severe problems.

If one, however, looks at the intradialytic levels, the average prevailing level of carnitine in the intradialytic period, these levels are very low and indeed, they are comparable to what one sees in the secondary carnitine deficiency of Fanconi syndrome and in primary carnitine deficiency, which as Dr. Kopple points out, is a deadly disease.

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It was based upon this analysis which had not really been done before, done by Evans in 2000, that the FDA concluded that the levels observed in dialysis patients were important to be treated, because of how low they actually are.

Are there clinical correlations to low plasma carnitine levels? Absolutely. These are a number of them. Van Es was able to actually devise an equation by which he could predict the ejection fraction from the plasma through carnitine level. Hiatt found a correlation between muscle carnitine content and exercise performance. Correlations have been found for low functional activity scales, for hypotension during dialysis, for indices of congestive heart failure by Kudoh, and for red cell indices as well.

Now, based on the DOQI report and what the DOQI considered reasonable, recognizing the

heterogeneity of the clinical data, which is a problem in this field, it is a problem in many nephrology studies, and clinical nephrologists have to kind of be like gardeners, we have to go through the weeds and try to find what is there in order to treat our patients.

However, based upon that as well as the

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recommendations from the expert panel of 1993 convened by the American Association of Kidney Patients but actually containing professors of nephrology, deans of medical schools who reviewed the literature, these are the indications that seemed to be agreed upon in those two studies for the use of carnitine. They include cardiomyopathy, dialysis arrhythmias and hypotension, skeletal muscle weakness, and anemia.

Please note that hyperlipidemia is not there. In 1993 the expert well recognized that this was not a consistent benefit and really, hyperlipidemia is not an indication for the use of carnitine, and I would shelve that as a waist of time to be spending your time with.

Now, what I would like to try to show you is that if we look at the data, and as I said, Dr. Klassen did a very nice review, what I would like to do is a little bit differently just tabulate the data and looking at specific clinical features that help to distinguish studies that were positive from studies that were negative. And by looking at those clinical features, we can develop guidelines for the responsible use of carnitine.

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These guidelines basically are that one must objectively document the condition for which carnitine is being prescribed, applying clear and defined standards for diagnosis. One must have an appropriate differential diagnosis for the indicating condition. You have to document prior use of appropriate conventional therapies for the

indicated condition. Carnitine, and this is very important, must be given for an adequate duration and use of intravenous carnitine is preferred for date that I will show you.

And because of the heterogeneity, and we can't get away from this, this is a drug that does not work for all the patient, even all the patients with the indications. We have to have a mechanism by which we can reevaluate by appropriate means whether the indication has been improved and only if improvement has occurred should we be continuing in this therapy.

I think it's important to realize, this was well summarized by Dr. Chertow, that the conditions for which levo-carnitine are being advocated are life threatening conditions. These are not trivial conditions. The life expectancy of a patient with congestive heart failure on

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dialysis is two and a half years. The point, and cardiomyopathy is the major cause of death in dialysis patients. Arrhythmias are a major and contribute to many deaths. Intradialytic hypotension not only has the side effects of MIs and strokes on dialysis, but also has the side effect of underdialysis due to an inability to deliver the actual prescription.

Muscle function is often underemphasized in its importance. 30 percent of dialysis patients cannot even perform their proper better washing and their proper toilet, and they're stuck in these lives. Low physical function moreover, in dialysis patients has been shown to double mortality and increase hospitalization by 50 percent. And muscle strength is the principal component of activities of daily living.

Muscle cramps are important because they also interfere with the delivery of adequate dialysis, which DOQI guidelines have clearly shown is connected to morbidities and mortalities.

Anemia is of great importance. For

every decrease of hemoglobin of one gram per deciliter, the risk of cardiac death goes up by 14

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percent and congestive heart failure by 28 percent.

Now let's look, therefor, at the medical evidence in a somewhat different way. First of all, this is just a tabulation of studies that show benefit or lack of benefit for different parameters of cardiac function. This is ejection fraction and ejection fraction improved in some studies, and this includes by the way, fractional shortening as well because it measures the same type of thing, or no effect in some studies.

VO-2 max, absolutely right, this was a secondary analysis by Brass, but the secondary analysis did show a benefit, and Ahmad showed a benefit.

And if one looks at arrhythmias, there is a consistency in benefit that you can see in your studies with the proviso that Ahmad did admit he didn't have enough patients with arrhythmias to really study, and that was pointed out by Dr. Klassen very nicely.

Hypotension, yes. Does it belong in muscle, does it belong in heart? Well, most analyses of dialysis hypotension actually hold the heart more responsible than the muscle. If one

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looks at dialysis hypotension, the studies that have looked at that as a specific parameter have all showed benefit. One can see that the aggregate number of studies showed benefit.

But you have seen this data. The question is, what can we learn from the negative studies? What can we learn about how not to use carnitine? I want to show you, since the greatest controversy was on ejection fraction and fractional shortening, what distinguished the positive and negative studies? These are studies that were positive on the bottom and these were

negative studies on the top a far as improving these parameters. And what one sees is that in two of the negative studies, the patient started out with normal ejection fractions or normal fractional shortening. You cannot fix what is not broken.

In addition, if one looks at the duration of these negative studies and compares with the duration of the positive studies, these were short duration studies. If one then looks for example at Fricke, where patients did have low ejection fractions, it was only a two-month study. In addition, appropriate clinical exclusions were

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not made. Other conditions that could exacerbate congestive heart failure in our patients were not accounted for. So these elements need to be incorporated as general principles of use.

Let's look at the differences between the myopathy studies. What I have done here is divide the studies into those that used oral levo-carnitine and those that used IV levo-carnitine. Note that there are a lot of positive signs here, improvement, improvement, improvement. The problem is if one looks here at the oral studies, all of the improvement except for one transient, this was the Sloan study that showed improvement at three months but degradation at six months, all the improvement in the oral studies was in symptoms.

And as Dr. Metzger pointed out, if you count up the studies, yes, a lot of oral studies show improvement, but it's in symptoms in these patients. The problem is that symptoms may not be -- we all worry about what the patient says when the doctor asks the patient, are you feeling better? Dialysis patients are very cooperative and they like to think they are saying what the doctor wants to hear. Now the problem is that

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symptoms have also been shown -- Ahmad, for

example, showed that intradialysis asthenia and post-dialysis asthenia, the symptom of just not feeling very good, improved in the placebo group as well. So our patients do respond to hope and something being done, so symptoms may not be as reliable.

Let's look at objective functional data, structural data, and data having to do with activities of daily living which have been shown to correlate with mortality and hospitalization both in dialysis and nondialysis patients. Here one sees that the data in support of objective and structural improvement is entirely from use of intravenous carnitine, and if one analyzes there this pattern, one sees that there is a significant difference in the bodies of evidence supporting one or the other, whether you use the oral or whether you use the IV.

In addition, if you look at the duration of studies here that are positive, they are considerable longer than the studies here. The six-month study using oral carnitine, as stated, was actually, the patients actually ended up worse. So longer term use and use of the

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intravenous form correlates with objective and structural improvement when one looks at these studies.

Anemia is a little bit simpler because we looked at the randomized control trials, the same ones that DOQI looked at, they only wanted to look at the RCTs, and if you look, all three RCTs, actually this was looking at EPO resistance. Now you can't, you're not going to detect a change in hematocrit if you're adjusting the EPO down to maintain a certain hematocrit. The way these studies were performed is we say we want to keep the hematocrit at a certain amount of the hemoglobin and we're going to see how much EPO we have to use. Well, the three studies of EPO resistance actually were positive, they showed benefit in EPO resistance, they used IV carnitine.

The study by Trovato did not look at EPO resistance. This was done in 1982 before EPO was being used and so we can't say what oral levo-carnitine does for EPO resistance.

The one negative study, Nilsson-Ehle had two characteristics, clinical characteristics. Number one, it was only a six-week study. Number two, there was no accounting for iron status most

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importantly, B-12 status, folate status, and other co-factors for blood production, these were not included in that study. But in the studies that accounted for those factors that used IV carnitine, there was a consistent improvement in EPO resistance.

This brings up the issue of oral versus IV carnitine, since it seems to be important in muscle, it seems to be important in terms of blood. Now there is this issue of bioavailability. In normal patients, only 5 to 15 percent of oral levo-carnitine is absorbed. Now, this not only deprives the patient of the benefit of the medication; however, what's perhaps more worrisome is that the unabsorbed carnitine is susceptible to bacterial degradation with formation of possibly toxic metabolites which I will discuss.

The IV form has 100 percent bioavailability. Now, as bioavailability expresses itself, one actually compares a tissue and levels in oral versus IV treated patients. And I think the best study, if one looks at the muscle levels achieved with oral levo-carnitine, they are considerably lower than one achieves with

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IV levo-carnitine. The best way to look, though, is for the same period of time.

If one looks at Albertazzi's study over six months period of time achieving a level of 28 micromols per gram of NCP as opposed to Ahmad over the same period, 50; and Siami when he used over

six months, was 52.6. So even used over the same period, the tissues accumulate the carnitine to a substantially greater degree with IV than with oral.

Studies have directly compared the same parameter using IV and oral carnitine. If you look at studies of anthropometric improvement, which the DOQI nutritional guideline believed was a valid way of following patients nutritional status and muscular status. The Rogerson study looked at that using oral carnitine and the outcome was negative. The Ahmad study used IV, the outcome was positive.

Giovenali is very telling, because Giovenali had different arms in the way he gave carnitine to the patients over a six-month period, and then he measured isometric muscle strength by well validated measures. He found that the arm given oral carnitine had to statistically

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significant improvement in isometric muscle strength, whereas the arm given IV carnitine had statistically significant improvement.

The problem is, as we discussed in the table on skeletal myopathy, that the strength of evidence for the benefit of oral carnitine is not as great as the strength of evidence for the benefit of IV if you accept the fact that mere symptomatic improvement is not as predictive. Improvements in activities of daily living have been well correlated to mortality and hospitalization, there are numerous studies showing that. This is not true with symptoms. And as I say, placebos improve symptoms as well.

No study using oral carnitine has shown the improvement in objective or structural parameters of muscle function either because they weren't examined or were shown not to improve. Oral studies have shown improvement only in subjective symptoms. Moreover, there are far fewer long-term studies with oral levo-carnitine and our patients are with us for the long haul

primarily, especially in the age of transplants. Patients are on dialysis for years.

And only one study using oral carnitine

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alone for muscle weakness, looking at muscle weakness, lasted greater than two months, and that study showed a negative outcome. There have been five studies using IV carnitine alone for this purpose lasting greater than six months.

In randomized control trials, the largest randomized control trial of Ahmad showed -- I'm sorry -- the largest randomized control oral study of Sloan showed initial improvement followed by deterioration in general health, mental health and vitality at six months. They patients ended up worse than they began.

With IV, the Ahmad study, randomized control trial, six months, showed benefit in a number of parameters, not only symptoms and dialytic morbidities by symptoms, but improvements in anthropometric measures, VO-2 max, with no deterioration in clinical condition noted with the use of IV carnitine. So there is a difference in the findings.

Why is there a difference? Well, there are toxicity issues and we have to address these. The toxicity issues relate to the different ways in which oral and IV carnitine are metabolized. Oral carnitine is metabolized to form

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trimethylamine, dimethylamine and N-nitroso-dimethylamine. IV carnitine directly enters the blood stream. The renal failure makes this a more important issue because usually trimethylamine is eliminated ultimately by the kidney and this doesn't happen in our patients, and dialysis patients have clinically been shown to have higher plasma levels of trimethylamine, dimethylamine and N-nitroso-dimethylamine.

Why is this a problem?

N-nitroso-dimethylamine is a potent carcinogen in

humans and many other species. TMA and DMA are known to be teratogenic, inhibiting production of DNA, RNA and protein. Increased plasma TMA and DMA in dialysis patients correlates with neurological deterioration. This was clearly shown by Simenhoff in lengthening choice reaction times. Increased plasma TMA correlates with deterioration in the EEG in hemodialysis patients and TMA and DMA are responsible for malodorous uremic breath, which though it seems a trivial problem is a serious problem for our patients and is socially isolating.

I was hoping to go over some of the clinical algorithms that we use and I would be

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very happy to present those, this is a very limited time, but we have developed clinical algorithms in respect to the time problem, in which we can look at specific indications, the ways that they've been employed, these have been widely seen by the nephrology community, presented at the NKF and published, and I would be delighted to go over at least one of those to show how one can incorporate these clinical distinctions into a responsible policy of use, but I will only do that if you want me to. Thank you very much.

DR. TUNIS: We can certainly do that in response to specific questions during the open comment period, depending on the panel's interest in that, but we do have some time for questions.

DR. HOLOHAN: I have one. I believe you said cardiomyopathy is the major cause of death in dialysis patients. Can you define what you mean by cardiomyopathy?

DR. SCHREIBER: I'm sorry. Congestive heart failure. It's present in 42 percent; if you look at all dialysis patients, 42 percent have congestive heart failure. It was pointed out by Dr. Chertow that 10 percent of all hospitalizations --

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DR. HOLOHAN: I understand that, I'm just trying to clarify. You said cardiomyopathy.
DR. SCHREIBER: Right. We tent to interplay terms.
DR. HOLOHAN: Okay.
MR. SUGARMAN: Would it not be relatively easy to do a retrospective analysis of mortality from cardiac disease in patients who are on carnitine versus patients who are not?
DR. SCHREIBER: First of all, there is retrospective data which will be presented later in this discussion that I am aware of, and as far as would it be easy, well, you could certainly do that analysis. You would have to first of all make sure that the patients were properly chosen for the use of carnitine therapy. I think part of the problem has been, again, if you see that patients are given carnitine for, who don't have abnormal ejection fractions, you see, if makes it more difficult to know whether the carnitine really had benefit or not. On the other hand, if you don't know if those patients were not given carnitine for other factors, I think you could do that and we have some data that would be important to see in that regard.

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MR. SUGARMAN: But it's not been done as a published trial. I mean, retrospective analysis, I think would be fairly easy.
I guess my other question is that Sigma Tau is probably in the best position to do a head to head trial comparing oral versus IV, that would be relatively simple. I'm not talking about a placebo versus treatment trial, I'm talking about a head to head with two drugs that are currently approved, at least FDA approved, and that hasn't been done.
DR. SCHREIBER: I would like to address that briefly because I work with Dr. Simenhoff. Dr. Simenhoff is the father, without making him seem too old, he is the father and grandfather of trimethylamines in dialysis. And Dr. Simenhoff

and I have been trying for quite some time now to just do the simple thing of administering oral carnitine and developing a curve of the trimethylamine amounts with the oral carnitine administration, and two institutional review boards have not allowed us to do that because of what they consider to already be evidence that these metabolites are toxic in dialysis patients. So I think that my own experience with that is

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that people are aware who review these things that trimethylamines do correlate with a number of problems, so it's actually been difficult to get permission to actually do, to actually be administering oral carnitine.

I find it ironic that we're talking about possible having that as a preferred form and I can't get two institutional review boards to allow me to do it for a month in dialysis patients. What Sigma Tau is in a position to do, I'm a clinical nephrologist and you'd have to ask them what they are in a position to do.

DR. METZGER: I might be able to help with that. The Trovato study in 1982 in Italy, you mentioned that all of the oral studies were symptomatic studies. The Trovato study was a measurement of RBC with reference to anemia. That lasted 12 months and it showed a definite improvement in RBC survival progressively over the 12 months, and interestingly, the oral form of the carnitine was supplied by Sigma Tau in Rome, Italy.

DR. SCHREIBER: Yes. I would like to clarify. When I was talking about that specific aspect, I was talking about skeletal myopathy.

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When I was distinguishing objective from subjective, that was in the context of skeletal myopathy. I do want to point out that there have been studies giving oral carnitine for longer than six months; however, they did not do a systematic

analysis as done in the Sloan study using SF-36 at the end of the patient's health status. They were looking at one parameter as you say, the hematologic parameter or cardiac parameter, but did not do a systematic analysis of health status at the even. For that study, that's why the Sloan study is unique in that regard.

But the comments about objective and subjective really refer to skeletal myopathy.

DR. TUNIS: Maybe one more question now, and then the rest we can save for the committee deliberation period. Go ahead, Commissioner Grant.

COMMISSIONER GRANT: Yes, I have two sort of related questions.

The first is, I just want a common sense understanding as a clinician, particularly in light of the FDA letter, which seems to say basically as an end in itself, the presence of L-carnitine is good, but then proceeds to

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distinguish what the evidence did not show, certain clinical issues. In your clinical experience, what do you use this for? Without getting into the elaborate protocol, but what do you find it useful for?

DR. SCHREIBER: What we use it for is cardiomyopathy or congestive heart failure that has not be responsive to the usual therapies, skeletal muscle weakness having a significant impact on the patient's health. If the patient's life is being limited by his Alzheimer's disease, not his skeletal muscle weakness, we don't -- you know, we have to see what will the patient get by having stronger skeletal muscles. And skeletal muscle weakness having significant impact that has not been adequately responsive to improving the anemia, improving the dialysis, et cetera.

COMMISSIONER GRANT: So while you may be parsing the various studies, there may not be the data to show that, is that your clinical experience, that it does help in those areas?

DR. SCHREIBER: Well, what I tried to show is that in these studies --
COMMISSIONER GRANT: I'm not talking about studies, I'm just -- your clinical

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experience is however it's working or not working, whatever the mechanism is, you have had experience that it seems to be doing something.
DR. SCHREIBER: Right. I have had many years, and I will tell you that you have to use it for the right indications. If you take carnitine and you throw it, you know, you've got mixers in the back room that mix your dialysate, you can't just throw it in the mixer and give it to everybody, because you're not going to see an aggregate change. What you have to do is give it to people with the proper indications, number one.
Number two, you have to make sure that you've improved everything else, that you're doing good dialysis and that you're treating everything else. And if you do that, you give it for the proper indications, you treat everything else and you give it for a long enough period of time, the reason I'm here today is because of the improvement that I have seen. A nephrologist is only as good as his tools.
COMMISSIONER GRANT: Thank you.
DR. TUNIS: Dr. Schreiber, the last thing is, I may have missed it, but could you just for the record again state any financial

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relationships you have related to Sigma Tau or others?
DR. SCHREIBER: Right, I'm sorry. I thought Mr. Mehrling had covered that. Yes. I have been paid for the time that I give Sigma Tau coming down here and when I do consulting work for them, I get paid for that time.
DR. TUNIS: Thanks, and you will be around for the rest of the day for any additional questions?

DR. SCHREIBER: Absolutely.
DR. TUNIS: Very good. I would like to move on at this point to Dr. Kadree's presentation and then we will have a brief break after that to fix our AV system.
Maybe while we're waiting, I didn't know if Mr. Mehrling had any comment related to Dr. Sugarman's question about the clinical trial of IV versus PO, did you want to make any comment about that?
MR. MEHRLING: We have been looking at this since 1982. We have done an awful lot of work between then and now on the product, and it's the opinion of the company with the advanced technology to measure both serum and tissue

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concentrations, that between the ability to achieve significant tissue concentrations as well as the potential and the unknown with the metabolites that are formed, we don't think it's a very good decision to pursue oral.
DR. TUNIS: And can you describe a little further the nature -- you had mentioned something about working with the FDA to develop a precaution. Is the precaution that you are trying to develop related to the dimethylamine, trimethylamine?
MR. MERHLING: It is. If you'd like, I can read exactly what it is. It is the same issues, it relates to the metabolites that are formed and the potential physioneurologic complications in the ESRD population.
DR. HOLOHAN: You said that is being submitted to the FDA?
MR. MEHRLING: It is at the FDA, yes, sir, as a change in effect for the package insert.
DR. HOLOHAN: And the FDA has agreed that this is appropriate?
MR. MEHRLING: In a situation where a safety consideration is made, it's unlikely that if a manufacturer submits that, unless there is a

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tremendous concern that it is irrational, that they will accept that, and I think the scientific review that accompanies that would be a reasonable thing for an unknown.

MR. SUGARMAN: Why is that not a concern for the other --

MR. MEHRLING: Indications for which the PO is used? You need to excrete the metabolites, number one. The liver will do the breakdown and then the kidney excretes it. If you have normal kidney function, it will be excreted.

DR. TUNIS: We will get back into this more later, but I was filling time, but thanks.

DR. KADREE: Good morning, everyone. There is never a presentation where there isn't an AV problem, all of my experience in presentations. Anyway, I am the medical director of Part A Medicare for Blue Cross/Blue Shield of Georgia, and I'm also a member of the ESRD work group that represents a conglomeration of the fiscal intermediaries for HCFA who have a significant number of ESRD patients under their jurisdictions.

Just to give you a little bit of a background, Blue Cross/Blue Shield Georgia has been a fiscal intermediary for HCFA for

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approximately 30 years, and as such is currently one of the major FIs for many dialysis facilities. In fact, we provide services for dialysis facilities in about 34 states around the country. So, looking at ESRD issues is definitely very important to us and we do monitor dialysis services in particular.

Around the middle of 1997, which was before my time, before my joining Blue Cross/Blue Shield of Georgia, one of the nurses doing medical review of ESRD claims noted that carnitine was cropping up quite frequently, and so that triggered the utilization, and here we see that between January and June of 1998, approximately 2 million was billed for about a thousand patients,

and this doubled in the subsequent six months, and if you compare the data for 1998 to 1999, you had a 2.5 factor increase in the amount of billing for carnitine.

And this is all before formal FDA approval of Carnitor for ESRD patients. If one were to look at the billed charges for individual patients for Carnitor alone, just looking at how much was billed for Carnitor, and comparing it to all other drugs that are billed outside of the

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competent rate for ESRD patients, and I include erythropoietin, which as everyone knows is quite expensive, we still find that billed charges for Carnitor is 1.13 times that for all other drugs, so we can see that this presents a significant issue for us.

As a result of the examination of the utilization in 1998 work was begun in developing a local medical policy, and the process took about 18 months all together, resulting in a draft policy that reflected input by numerous nephrologists, other fiscal intermediaries other than Blue Cross/Blue Shield of Georgia, as well as a review by Part B, the carrier advisory committee, because fiscal intermediaries don't usually have formal advisory committees looking at these types of issues. And the decision was made that the data available supporting the medical necessity of intravenous carnitine was inadequate and as such, this is an ESRD population that is, and as such, the only coverage for intravenous carnitine would be in patients with an inborn error in metabolism where the data is much stronger this is indeed beneficial and where indeed you do have life threatening consequences

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when carnitine is not administered, so refocusing on the ESRD patients and whether this drug is indeed necessary given in the intravenous form to these patients.

In December of 1999, the FDA did approve intravenous Carnitor to use in ESRD patients, and basically the package insert for the drug states that intravenous Carnitor does indeed raise plasma carnitine levels, which is not astounding, but the package insert very interestingly goes on to state that the effects of supplemental carnitine on modifying or relieving signs and symptoms of carnitine deficiency as well as clinical outcomes in the ESRD population have not yet been determined, and to me that's a very profound statement.

Well, for Y2K, the fiscal intermediaries, and remember, the fiscal intermediaries are the ones who tend to, are the contractors who tend to have to deal with ESRD claims, the fiscal intermediaries have had a high volume of ESRD patients, or had Carnitor noncoverage policies, or known to be developing policies, were bombarded with form letters from providers as well as Congressional inquiries.

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In the fall of 2000, the fiscal intermediaries who had a high volume of ESRD patients decided to form a work group in an attempt to provide some kind of common ground, a sort of think tank for development of policies that primarily affect ESRD clients, and not surprisingly, carnitine is just one of them, and actually carnitine is just one of the issues that we were concerned about.

An extensive reassessment of the literature on carnitine was done in the fall of 2000 and again, the same conclusion arrived at, that the medical necessity for intravenous carnitine in ESRD patients was not clearly supported.

The issue was raised to a national level, so here we are today again trying to address this very important issue.

And just to reiterate what Dr. Whyte has already said, basically you need to establish

whether the available evidence makes a strong case for the effectiveness of levo-carnitine in ESRD patients and for us of course, we are referring primarily to the use of intravenous form of carnitine. Is it medically necessary to

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replenish plasma carnitine and muscle carnitine in the intravenous form.

The DOQI group, as was mentioned earlier, they did review carnitine, and with the wealth of experts in that group, it's not surprising that whatever recommendations they make are looked at seriously in terms of this type of review. And they indicated that the data was insufficient to support the routine use of levo-carnitine. And they did go further and say there may be some patients who may benefit from carnitine supplementation after all other interventions have failed. However, they were also very strong on the fact that additional clinical trials need to be done to resolve some very critical issues.

Blue Cross/Blue Shield of Georgia did offer directly Sigma Tau, the manufacturer, the opportunity to act as a facilitator for such studies, because we have a large population and we felt that we could used as a resource to assist them in answering some of these questions, because we are indeed concerned that if this drug is of value to these patients that we are making the correct decision in terms of administering it or

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not.

Specific recommendations that DOQI had made with regard to the additional studies needed, with regards to erythropoietin resistant anemia, carefully accounting for anticipated differences in response based on factors such as iron stores, inflammatory mediators, as we well know, carnitine deficiency is not usually highlighted as a primary reason for EPO resistant anemia and you absolutely

have to look at some of the probable more common causes before assuming that it may be due to carnitine deficiency.

Also using an outcomes approach, identifying patient subgroups who are likely to respond to carnitine for one or more of its proposed indications, doing a randomized clinical trial of carnitine in dialysis dependent patients who have cardiomyopathy and reduced ejection fraction, and doing randomized clinical trials for the treatment of hyperlipidemia, which is also something that is a fairly hot topic.

Now the ESRD work group, as I said, has been looking at this issue, and some of the crucial questions that we've asked is first of all, how does one actually define carnitine

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deficiency? Carnitine deficiency is most commonly defined as a state of carnitine concentration in plasma or tissue that is below the requirement for the normal function of the organs. However, based on the literature, the clinical significance of carnitine deficiency lies within the disturbance of the balance between the functional carnitine requirements and actual carnitine levels. So it's not simply a straightforward relationship.

Of course the, in the studies, most of the studies used, and also in the package insert, the modality used to determine carnitine deficiency clinically has been the objective modality which has been the plasma carnitine level. And as I said, it's well-known that that's not ideal. And certainly when we look at plasma carnitine levels as a reflection of what's going on in the muscle, I think we have even more problems, because the skeletal muscle and cardiac muscle account for 98 percent or more of the carnitine body scores and we know that the level of carnitine in muscle is about 50 to 100 times that of plasma.

Furthermore, although we do not have a good handle on the pharmacokinetics of carnitine,

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we know that the plasma carnitine turnover in skeletal muscle is about five to seven days and if you look at the total body turnover of carnitine, it's about 65 days. So, you know, that's very significant in terms of if we were reflecting on a patient who has muscle problems related potentially to carnitine deficiency whether it's necessary to give the drug in an intravenous form, whether that's actually particularly useful. Yes, you will raise plasma carnitine levels, but are you actually going to arrive at, are you going to actually increase the muscle levels any more rapidly.

I also want to add that in terms of the pharmacokinetics, it's pretty well established now that uptake of carnitine from plasma into muscle is transport, it's carrier mediated, which means that it's going to be saturated, so you really after a finite concentration of carnitine, you do not increase the amount of transfer of carnitine from the plasma to muscle any more rapidly.

And just one more piece about the muscle and carnitine issue, and that is, we were told earlier that the major importance of carnitine in the body is the transport of fatty

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acids from the cytosol into mitochondria, where fatty acid observation occurs, and that in turn leads to production of energy. And this indeed is the primary source of energy for skeletal muscle.

Therefore, one might expect that the levels of fatty add acid, oxidation and skeletal muscle might be a good surrogate marker of physiologically significant carnitine deficiency. Now only a few studies have attempted to examine the functional effect of subnormal muscle carnitine levels and the data that is available does suggest that carnitine levels would have to be severely depleted before fatty acid oxidation is impaired and in fact, in one study by

(inaudible), patients with muscle carnitine levels as low as 1.5 percent that of the norm, may not have any significant signs of myopathy, and that level of depletion is not usually observed in patients on hemodialysis.

Siami, which is one of the studies that you all have reviewed, he conducted a double blind study that specifically evaluated the effects of intravenous carnitine on fatty acid oxidation in muscle. 14 patients on hemodialysis were given two grams of carnitine post-dialysis three times a

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week for six months. Prior to the initiation of carnitine and at the end of the study, muscle biopsies were performed on 13 patients. Muscle biopsy was also obtained from six healthy controls. Fatty acid oxidation and carnitine levels were measured in each muscle biopsy. It was noted that fatty acid oxidation was significantly lower in the carnitine treated hemodialysis patients than the controls. However, of great interest, the observation that in spite of the supplemental carnitine tripling the carnitine concentration in muscle, this did not lead to any significant increase in fatty acid oxidation levels. Therefore, again, there is not a simple equation in terms of the levels of carnitine in muscle and fatty acid oxidation in patients with ESRD disease, so this really needs to be looked at very closely.

Now what about the specific signs and symptoms of carnitine deficiency? If you're going to administer a drug, hopefully you have some means of recognizing when the patient may in fact be able to benefit from that. Well, all of the indications for carnitine, you know, weakness, easy fatiguability, post-hemodialysis asthenia,

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intradialytic hypotension, chest pain, muscle cramps, are very common complaints among hemodialysis patient and this is in fact related

in large part to the multiple comorbidities that these patients suffer as a result of their kidney disease and their endocrine abnormalities that may result from that, never mind the fact that they are usually malnourished, et cetera, et cetera, so the list goes on.

So again, we don't have any true and tried signs and symptoms that we can relate specifically to carnitine deficiency. And remember now that also the plasma levels of carnitine does not help us very much in terms of identifying someone who is truly carnitine deficient.

Other issues raised by the ESRD work group. We know that the oral drug does replenish plasma carnitine levels satisfactorily, so in what instances then does it become medically necessary to administer the intravenous drug? And if indeed you do use the intravenous drug, what are your end points? Again, the ESRD work group states, if it should ever become necessary to administer carnitine intravenously, might it not be more

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appropriate to consider it as just another part of the dialysis service and so cover it under the competent rate?

What is the true clinical significance of carnitine deficiency? I think I have pretty much gone over that particular aspect. But another problem that we have is, what is actually the dose of carnitine that is physiologically appropriate? Studies have shown -- currently the recommended dosing is 10 to 20 milligrams per kilogram. However, studies have shown that doses as low as 2 to 3 milligrams per kilogram given intravenously are very adequate, and they also mention the aspect about saturation of the carrier proteins.

So you know, one is hard pressed to determine how to administer the drug appropriately when we're not even sure what the correct dosages should be. We know that current intravenous

dosing, dosing at the current recommended intravenous dosages does lead to supernormal levels of carnitine. What are the long-term effects of this?

Carnitine is actually a metacholine and combined to acidize choline receptors. Are we

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going to start seeing, if we decide to use the drug liberally, are we going to start seeing side effects of the drug related to this type of binding? Again, we need to answer questions like this.

Furthermore, we have to make absolutely sure that patients on dialysis are properly evaluated in terms of their coexisting morbidities before one considers adding yet another drug whose medical effectiveness is somewhat questionable. You know, we have to make sure that we are looking at it closely, and I can tell you from direct experience of evaluating claims and so forth that usually the rationale for administering carnitine is not well stated, it just seems like it's just given without much attention to the reason, and while I'm quite sure that for those practitioners who are at the forefront in this, that they are using a rational process to do it. This is not the case for the majority of practitioners in the field.

And as I say, I know for a fact that many times, and this is not just applying to carnitine but even drugs such as erythropoietin and so forth, that reasons for the patient having

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problems are not always examined in administering the drugs. So, I am coming to the end.

In approving drugs for coverage, should we deviate from the clinical efficacy and outcomes data in determining medical necessity? And last, but by no means least, where do we go from here? Hopefully, today's session will allow us to arrive at some consensus in terms of the appropriate

decision on this issue, and I speak on behalf of the ESRD work group when I say that the evidence supporting the medical necessity of intravenous carnitine at the time is not substantial and therefore, care must be taken to insure that whatever decision is arrived at does not ignore this fact because of potential political or pharmaceutical company pressure. Thank you very much.

DR. TUNIS: Thanks, Dr. Kadree. It looks like there's a -- maybe if we could just have a couple questions and then, you will be around for the rest of the day as well?

DR. KADREE: Yes.

DR. TUNIS: So we will try to get back on track. Go ahead, Dr. Metzger.

DR. METZGER: Doctor, you're the

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medical director of Georgia?

DR. KADREE: Yes.

DR. METZGER: Considering all you've presented today, including the great many steps of fatty acid oxidation, isn't it your policy is that allows for coverage of that in the April and the May '01 policy?

DR. KADREE: Right. We had been barraged by a lot of requests pertaining to noncoverage and so forth, and it was decided that we would call a panel, put a panel together and take a look at this issue, and based on the results of the panel, it was decided that we would liberalize the policy.

If you look at the policy very closely though, you realize that there are some very very stringent requirements that need to be met, and we feel that, well first of all, all claims for carnitine is being subject to medical review, and we feel that as I said earlier, there probably is a subset of patients who can benefit from this drug, but there are lots of questions that are unanswered. I feel that the criteria that has been developed by Blue Cross/Blue Shield of

Georgia is strong enough and stringent enough to

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insure that when it is administered, it is indeed the appropriate thing to do. So this, as I say, was a liberalization of the policy and certainly not meant to imply that it should be something that is used routinely.

DR. TUNIS: Go ahead, Mitch.

MR. SUGARMAN: Thanks, Dr. Kadree. Since you raise the issue just in your fourth and fifth slide where you look at utilization, it looks like $9 million from July to December '99, and 1.13 times for all other drugs, was that using oral or IV?

DR. KADREE: Intravenous, because Medicare does not cover oral. This is strictly intravenous.

MR. SUGARMAN: And it would be significantly different if it were oral?

DR. KADREE: I'm sorry?

MR. SUGARMAN: If there was a Medicare drug benefit and you covered the oral dose, it would be a significantly different number I suspect.

DR. KADREE: Yes, I imagine so.

MR. SUGARMAN: Thanks.

DR. TUNIS: Okay. We will now take a

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ten-minute break, and we will start exactly in ten minutes. For the later sessions, we will adhere brutally to our assigned times.

(Break.)

MS. LONG: Okay. We are going to continue now with scheduled public comments. The next speaker is Dr. Jill Lindberg. And just as a reminder for the speakers, there is a light up at the podium that will flash when you have, it will say sum up, and then when it does go red, that's it, it will cut off. Thank you.

DR. LINDBERG: My pleasure to be here. I'm a nephrologist at Ochsner Clinic, New Orleans.

Some of my patients are on carnitine and I have a video for each of you. I'm here because of them, because clinically it has made such a difference in their life and also their quality of life, and we will pass those videos out. The video was produced by Ochsner, not by Sigma Tau.

My financial interest in Sigma Tau is I am paid for coming here, consulting and for speaking, but -- and I have this documented, we have a healthy start fund for patient education. I have been a leader in the nation in developing healthy start programs to keep patients off

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dialysis with creatinines of 1.5 and greater, and to educate them very well before dialysis, and we have decreased hospitalization costs three months before and after the start of dialysis in the 174 patients who have gone through the program in the last two years by $22,000 per patient over six months. So, we didn't have funding for that, so my honoraria go into that fund.

I want to tell a little story about studies in dialysis patients before I get started. Studies in dialysis patients are tough. I think we've seen that. It's really hard, you're very restricted in the control arm and the treatment arm because they are so sick. And often they end early, they are closed, there's not enough recruitment because patients don't want to be bothered, they are very very hard to do.

One example. We have been giving calcium binders to bind phosphate in dialysis patients for years and all of a sudden we saw this high increase in calcification in our patients. Our patients die of cardiovascular disease, and one of the reasons is they come to us too late with severe left ventricular hypertrophy which then develops into congestive heart failure and

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end stage cardiomyopathy, and the other reason is the calcification.

And it wasn't until Jeffrey Block took 6,405 patients from the morbidity and mortality study and the case mixed study and looked at that data retrospectively, as you have suggested, and found that phosphorus levels of 7 and greater have a 34 percent higher risk of mortality. Everybody was saying oh, if you have a high phosphorus level, a little bone disease, a little itching, huh-uh, calcium phosphorus products, even in our children on dialysis, if you have a high calcium phosphorus product, because we've been feeding our patient calcium as binder, and you can't get rid of it, you will have a scan of your chest that will have a hundred times the calcium in it as another child. So, we had to find this out with retrospective review and that's what I'm going to present to you today.

(Pause for audiovisual support.)

The mortality rate due to cardiovascular disease is 10 to 20 times higher among ESRD patients compared to the general population. What this retrospective review did is to look at changes in morbidity, hospitalizations,

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mortality, laboratory test results and drug dosing of epogen and iron before and after exposure to carnitine.

This isn't it.

(Pause for audiovisual support.)

The objective of this retrospective review of data, the database, is to describe changes in morbidity, hospitalizations, mortality, laboratory test results, drug dosing with epogen and iron before and after exposure to carnitine. We used a database from Fresenius Medical Care, it's a well known database and it's been used for many studies retrospectively of morbidity and mortality in our patient population. The data integrity was managed by statisticians from Emory University and Tulane.

The analytic strategy is to describe the cohort of 12,477 patients and changes in the

outcomes measured before and during carnitine administration. We're going to separate into Group 1 and Group 2; the 8,100 patients who received carnitine for greater than three months, Group 1, compared to 4,377 who received carnitine for less than three months, compare probability of hospitalizations, cardiac events while controlling

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for other variables, and difference in laboratory results were also compared in these patients.

The patients, the 8,100 received IV carnitine for at least three months, and the 4,377, Group 2, for less than three months. The reason for dividing the patients was to have two groups with comparable baseline characteristics since both groups had indications for the initiation of IV carnitine.

IV carnitine is not for everybody, you have to have a specific indication to order it. I don't even, my nurses won't even put it on the, hang it on the machine if it's not.

Outcomes measured, hospitalization rates, and frequency of specific morbidities for which patients were hospitalized, mortality and various lab values, which I'll go over in a minute.

This is very important, the descriptive statistics, the mean values, this is during the period they had, the patients 8,100 were on 13 months. You need to be on carnitine, in my experience, at least four to five months to see changes. The ones who were on it less than three months were only on 1.3 months. Time on dialysis

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before carnitine, 34 months and 32 months, that's very important. I see these patients as the babies that are born, like floppy baby syndrome. They are circling the drain, you've improved their KT/V, you've improved their EPO dose and you're just not getting anywhere, and they are circulating the drain, and it's not your whole

population.

Diabetics were equal, females were equal, and deaths and hospitalizations, actually this was a sicker group, which is not unexpected with patients who received it for a longer period of time. Average hospitalization rate for any reason of greater than 24 hours per thousand person years, this any reason and greater than 24 hours, was significantly different in Group 1, pardon me, Group 2 -- Group 1, the 8,100 patients, versus Group 2, the patients who had received carnitine for less than three months, an average of 1.3 months. Group 1 had a 20 percent greater likelihood of being hospitalized for any reason than Group 2, without adjustment for confounding variables.

These are the confounding variables. These are often used, this is fairly standard in

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all of our retrospective dialysis data analysis, age, length of time on dialysis, diabetic status, adequacy of dialysis which we use URR, albumin, hemoglobin hematocrit, and epogen dosage.

We adjusted for that and we looked again. In Group 1, who had had carnitine for less than three months, again 1.3 months was the average, they are 1.3 times more likely to be hospitalized than Group 2 where again, the average carnitine was 13 months in this group. So when you adjust for these confounding variables it was even a more significant difference.

Similar results were shown for hospitalizations less than 24 hours with an adjusted odds ratio of 1.4. Why is that important? Very commonly dialysis patients end up in the hospital for 24 hours because they have hypotension on dialysis, we fix them, they go home the next day, or they're cramping, or we can't get the fluid off because their hearts are bad.

Average morbidity, ICD-9 event codes per thousand person years with Group 1 and Group 2, you can see there was a significant

difference in the hospitalizations of less than 24 hours, being much greater in Group 1, the ones who

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had only received 1.3 months of carnitine.

CHF was significantly greater, and fluid overload disorders, which of course is classic when you can't get the fluid off these patients.

Logistic regression, patients in Group 1 were 1.37 times more likely to have congestive heart failure than patients in Group 2. And here's mortality; the deaths in Group 1, the 4,377 patients, 1.3 months average, were 35 percent per thousand person years because we had to adjust for the time they received the carnitine, versus Group 2 that was 30 percent, and this was a significant difference. When you look at the average mortality rates for these two groups, the mortality rate, significant increase in mortality rate in Group 2, P less than .001.

Now, if you look at lab results, in using 8,100 patients, Group 2, there was a statistically significant increase in hematocrit, hemoglobin, red cell count and URR, as compared to the other group. In Group 2 patients beyond three months, the increase in hematocrit and hemoglobin was not fully accounted for by the increase in URR and average epogen doses, suggesting an effect of

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carnitine. The point is, I have two graphs that are in your handout, but I don't have time to go over them; it was actually a negative correlation, hemoglobin versus epogen, and hemoglobin versus URR, the point being that carnitine was having an effect here when you worked this out.

In summary, the use of IV carnitine by dialysis patients for greater than three months correlated to the following positive outcomes: Decreased rate of absolute hospitalizations, decreased rates of hospitalizations for cardiac morbidities, decreased death rate, increased

adequacy of dialysis, improved hemoglobin hematocrit.

And with that, I would like to end and tell you that I'm here. I'm supposed to be at a regional soccer tournament for my son, and I chose to come here because of my patients, and they are going to tell you about it when you look at the video.

DR. TUNIS: Thanks very much. I think we will hold all questions until the open panel deliberation when we can direct questions to any of the public speakers. Thanks.

MS. LONG: Okay. And the next speaker

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is Abbey Meyers. Following Abbey Meyers will be Dr. Paula Bonino.

MS. MEYERS: I don't have any slides, and you should be very grateful because I would really screw up this computer. My name is Abbey Meyers, I am the president of the National Association for Rare Disorders, which is known as NORD, and we represent over 6,000 different rare diseases. We are a nonprofit voluntary health agency dedicated to the identification, treatment and cure of orphan diseases.

The Federal Orphan Drug Act of 1983 defines an orphan disease or condition as any that affects fewer than 200,000 Americans. The Orphan Drug Act was created because prior to 1983, pharmaceutical companies did not want to develop drugs for low incidence health conditions because they were perceived to have little commercial value, and this amounts to subcategories of the dialysis market.

I am here today to speak on behalf of all orphan drugs and their need to be made available and reimbursed through all health care programs. While I will be speaking about Carnitor injection today, I would be just as enthusiastic

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in my support for any other orphan drug in a

similar situation.

I would like to also say that Sigma Tau is a very small company, you're not dealing with Bristol Myers here, and when you talk about doing a lot of extra studies, they are not going to happen, because they don't have the financial means as the larger companies do. If the manufacturer of Carnitor injection knew that Medicare would not reimburse for this treatment, they would not have spent the millions of dollars to get the drug approved for dialysis patients, and people who need dialysis would be medically disenfranchised.

Carnitor injection is the only product approved by the FDA for treatment of carnitine deficiency in end stage renal disease, and Carnitor injection is not approved for the treatment of myoglobinuria. Some of the Medicare carriers say that they will reimburse for, the fiscal intermediaries will reimburse for an unlabeled indication, myoglobinuria, but not for dialysis patients. It's incomprehensible and this should be corrected.

It's come to our attention that some

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people are even recommending the use of oral levo-carnitine in place of Carnitor injection. Oral levo-carnitine is not proven safe and effective for dialysis, and there is evidence that it may not be safe for that indication. Furthermore, it's unacceptable for anyone to suggest, as some fiscal intermediaries have, that an unregulated dietary supplement version of oral carnitine could substitute for the prescription carnitine injection. The FDA does not regulate dietary supplements and they are often subpotent. For dialysis patients, Carnitor injection is necessary to treat carnitine deficiency and oral carnitine may not be safe or effective, and is no other alternative.

On behalf of NORD, we ask you to consider reimbursement for Carnitor injection that

will allow physicians to determine the selection of appropriate treatment. When a manufacturer invests in research and development of an orphan drug, they know that the potential market for the treatment will be small. Nevertheless, they have to prove their drug is safe and effective for a particular indication, and the FDA confirms this by approving the drug for sale in the United

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States. Carnitine injection is not only proven safe and effective, it's the only compound approved and labeled by the FDA for treatment of carnitine deficiency in dialysis patients, so denying reimbursement for Carnitor injection in the dialysis population leaves no treatment options available for these patients and their physicians.

In my written statement, I explain that Sigma Tau will be covering my expenses for coming down here, and I'm very happy to be here and happy that you are holding public hearings to allow public input.

Dr. Kadree just brought up that it seems to be a financial problem, and we were active years ago when EPO was approved and believe it or not, and I find this incomprehensible, EPO came on the market as an orphan drug, and their negotiations with HCFA at the time was to settle on a price for the drug, on the premise that only something like 20 or 40 percent of dialysis patients would be taking the drug. And of course, we know that it's turned into one of the most profitable drugs in the world now, not just for the dialysis market, but for chemotherapy

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patients, et cetera. And I get the sense that HCFA would like to avoid another EPO debacle with this drug, that it's really a financial problem, that it's really not a medical problem, but to the patients it's a medical problem.

So I would suggest that you think,

number one, find a way so that carnitine IV or injectable will not be prescribed indiscriminately; there should be some laboratory tests that are required before a person qualifies for taking it. And then, that you try to negotiate a price with the company so that you will be able to project what your annual costs are going to be.

When I saw the slide that Dr. Kadree put up there amount the large amount of increase in this prescribing of this drug, I understand what your concerns are, but that's not the concerns of the patients. The patients are concern that they are treated appropriately and if there is a financial problem here that is stopping them from being treated appropriately, you have to handle it in a rational way so that you can understand what your costs are going to be.

We want you to endorse a policy for

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Carnitor injection and reaffirm the valid medical need of these patients. Thank you.

MS. LONG: Okay. We're going to move on to Dr. Paula Bonino. You will notice on the agenda, the next speaker was to be Dr. Suhail Ahmad. He isn't here today, so that's why we're moving ahead, and then the speaker following Dr. Bonino will be Carole Hernandez.

DR. BONINO: Good morning. While he's getting my laptop up, let me just say that I have one of those LMRPs that has myoglobinuria. Let me read you the definition of the ICD-9 code 791.3. myoglobinuria (carnitine polymethyl transferase deficiency). It is the only ICD-9 code available; we do not have any ability to make up these codes, this is the only code for carnitine deficiency.

So we have more problems in developing policies. I have many things I'd like to talk to you, just like everyone here today, I'm just going to give you one question that I would hope would be addressed at some point today because I'm having trouble understanding it. And that is that

75 percent of carnitine is taken in orally in the diet. Now I understand that primarily it comes from red meat and among the dialysis population,

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many of these patients are on protein restricted diets.

My concern about the discussion about the trimethylamine toxicity issue with oral Carnitor is, you know, we all take this in diet; we're talking about supernormal doses I would guess is what the issue is, and if we have an active metabolite that's toxic, does dialysis remove it? These patients are on dialysis three times a week; if the problem is their kidney function is impaired, isn't it being removed by the dialysis? And I don't know those answers. Okay.

I'm only going to focus on two issues, the considerations of the Medicare contractors employed by HCFA to develop local coverage decisions or policies, and I will try to slow down, and to review the experience with levo-carnitine in Pennsylvania. I will not review all the clinical issues. I am an internist and geriatrician, I do not currently have in my practice any patients on hemodialysis or receiving IV carnitine.

I will tell you also on my other disclaimers that there's no line in my budget and

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my contract with HCFA to pay for me to come here. That's why you don't see more CMDs from these contractors here today, we have no payment mechanism to come here. We have payment to support HCFA and we do that, and most of us have sent in written documentation on this issue to HCFA, but we are not paid to come and present.

Considerations that we have. LMRPs are administrative and educational tools that assist providers to submit claims correctly for payment. Their focus is on Section 1862(a)(1)(A) of the

Social Security Act, which is the reasonable and medically necessary section, and they have three major rules. They are to be consistent with national guidance, there isn't any for levo-carnitine and that's why we are here today. They are to be consistent with scientific evidence and clinical practice, and you've heard a lot today and I will tell you what Pennsylvania's clinicians have to say on this topic. And they are developed with input from medical professionals, which is why all the physicians and other clinicians are here today.

Further, the Medicare Program Integrity Manual, Chapter 1, section 2.3.1, further directs

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us to develop LMRP for those services that have demonstrated a significant risk to the Medicare trust funds. These include identified or potentially high dollar and/or high volume services. It doesn't mean we don't pay for them, it directs us to give guidance on what is appropriate to pay for and what is not.

As you have heard today, a prescription drug benefit for Medicare beneficiaries does not now exist, there is no payment for oral medications with a few exceptions related to cancer chemotherapy and others. That's one of the major reasons this issue came to the forefront.

For fiscal year 1998, we're turning now to Pennsylvania's experience, we looked at our overall data to see where our Medicare dollars were being spent in Pennsylvania. We had at that time 7,690 ESRD patients for whom we processed claims. The costs for everything related to those patients was more than $100 million. Of that, we found that intravenous drugs accounted for $16 million, and in 1998 prior to the FDA approval for this use, levo-carnitine accounted for 3.6 million of those $16 million. The other major players in the intravenous drug were the Vitamin D analogs

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and iron supplements; you all probably are aware that a lot of iron supplements are now covered by national coverage determinations, the Vitamin D we are all struggling with individually.

In 1998 we found that the use was extremely variable in the state of Pennsylvania. There were units that used it for everyone, units that never used it and units that used it for selected patients. Ten of the 174 hospitals in Pennsylvania at that time that we processed claims for used levo-carnitine in their treatment of ESRD patients and believe it or not, Pennsylvania is extremely rural.

Except for Pittsburgh and Philadelphia and maybe Harrisburg, it's a very rural state so in some areas, patients do get their chronic hemodialysis at the hospital. This is not just about acute care, these are chronic hemodialysis patients. Of the 96 freestanding dialysis units that we processed claims for at that time, 52 used the drugs, or a little over half. However, of those 62, 10 and 52, half of the people who used it used it for fewer than 10 patients, so it was clearly not the universal standard of care for all dialysis patients. In fact, the drug was used in

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only 717 of the 7,690 patients, or about 9 percent of the population.

A central issue of course that we're all talking about today is who needs it, is oral okay, if it's not okay how do we identify which patients need it, and one of the issues that we saw in Pennsylvania at the time was the desire on the part of a few folks to use it broadly for every patient on dialysis, not for the selected individuals that we've heard talked about this morning.

IV levo-carnitine represented 23 percent of all drug expenditures for these patients in Pennsylvania in 1998 prior to the approval for this use, while it was used in only 9 percent of those patients. If it were to be

used for every dialysis patient, we would be up to 230 percent of expenses. I don't mean to say that this is all about costs the, but to infer that cost bears no importance is not right either in the sense that the Medicare trust fund is a limited source of money and we have to be cautious about the implications so that when we develop policies, we try to develop them for clinically prudent, medically proven reasonable and necessary

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uses.

As with all drugs, no one's mentioned the side effects yet today. Seizures have been reported in patients taking levo-carnitine. I found the information about valproic interesting, and this is patients who do or do not have preexisting seizure activity, and it's been found with both the oral or IV form. In those patients who have preexisting seizure, an increase in frequency and/or severity has been reported.

We looked at the literature, you've all looked at it. At the time, the review revealed that oral carnitine might be helpful in the anemia question, and our review is that erythropoietin was better than carnitine at the time, although these issues of existence are coming up now, and erythropoietin of course was already covered.

So we went on to do our job and develop an LMRP that gave specific coverage guidelines. We talked to Pennsylvania's nephrology community, we talked to Pennsylvania's ESRD network. Pennsylvania's clinicians did not feel this was a drug that Medicare should be paying for at this time. Therefore, our indication is for the acute treatment of patients with the inborn error of

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metabolism that results in a carnitine deficiency either primary or secondary. It is not covered for the routine use for all ESRD patients in Pennsylvania.

LMRPs also, as you may or may not be

aware, have the ability to have medical exceptions requested. I'm afraid to put this slide up, because I also don't have a staff of people to answer the 3,000 mail requests I'm going to get tomorrow, but if I have 3,000 people in Pennsylvania that need this, I need to be hearing from them.

In fiscal year 1999, before the LRMP went into effect, you will notice that our 62 providers went up to 70, our 717 patients increased to 905, and we paid out $4.6 million for this drug. In fiscal year 2000, after the LMRP went into effect, 15 providers submitted claims for 55 patients, and they were paid. I have had not a single request for a medical exception since the day this policy went into effect.

From a clinical standpoint, these patients are young for Medicare, but they are frail. They have multiple serious illnesses. Proper medication use in this population is

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essential, and it's a valid quality of care issue. Your work for today is the work we've all described. Should we cover it, is it reasonable and medically necessary is the cornerstone of that argument and if indeed it is, can we identify who's going to benefit, should there be a requirement for a trial of oral, and we have to, I think, think about whether this is or is not the nation's standard of care.

MS. LONG: Thank you, Dr. Bonino. The next speaker is Carole Hernandez, and following Ms. Hernandez is Edwin Scott.

MS. HERNANDEZ: Let me say at the outset that my expenses to be here today from New Jersey are being reimbursed by Sigma Tau. Good morning.

I am glad I could arrange to be here today to relate how IV Carnitor has affected my life. I am a dialysis patient for close to 25 years. I have seen many things come and go, some good, like Carnitor, and some not so good, like

the Bentley button for hemodialysis.
I think it's significant when something comes along to improve the quality of life for dialysis patients. I know from personal

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experience Carnitor is that something. My quality of life directly affects a number of people and indirectly even more. I live with my husband of almost 29 years, a teenage niece, and a cat. I love them all and I do my best to take care of them if even in small ways.
I have restless leg syndrome. RLS is a problem that causes a crawling feeling in my legs that is only relieved by moving them. It according to NORD, the National Organization for Rare Disorders, typically occurs at sleep or rest, is chronic and progressive. This has been my experience for close to 40 years. According to the Awake magazine of 11/22/2000, RLS affects up to almost 15 percent of the U.S. population. Chronic disease may cause RLS symptoms, particularly kidney disease.
I was a young girl when symptoms started and it usually occurred late at night in the car, coming home from a family outing. I was told to sit still and behave, but I just have to shake my legs and change my position constantly. This was a rare occurrence back then that had no name, and has become chronic and progressive. Over the years, the episodes have become more

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frequent, they last longer and the symptoms are relentless.
Before Carnitor, IV Carnitor, my last experience with RLS had me barely going through the motions of life. I was awake every night walking, reading and rocking, writing letters while I moved my legs. I was given several medications, all one after the other. I was up to five. I was taking Ambien, Valium, Klonopin, Percocet and Elavil, all taken half an hour apart

from each other, so by three or four in the morning, I would finally go to sleep at the kitchen table or on the couch or in the rocking chair.

It was very upsetting to have my husband get up and down at night to check on me. It made me feel that I was causing him so much concern, it made me feel bad that I was causing him so much concern and loss of sleep. My mother would write me and say Carole, please stay away from the stairs while you're like that. I tried not to turn on too many lights and I learned to cry quietly. I was frustrated, depressed, and felt a burden on my husband.

I began to cut my dialysis treatment

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towards the last hour or hour and a half, because I was so restricted in movement I just felt like I could scream. They started to give me IV Valium, but that resulted in only maybe a five or ten-minute reprieve. Then my doctor, Mohammed Huq, decided to start me on IV Carnitor with the hope of helping my RLS.

We started out with a half a gram and increased to 2 grams after each treatment three times a week. My restless leg syndrome was gone, and it did not recur the years that I was on IV Carnitor. I had no episodes. My cardiac arrhythmias also went away completely. That is significant because in the book The Wisdom of Menopause, by Christine Northrup, she writes, "Carnitine helps prevent heart disease, helping to prevent cardiac arrhythmias" what a blessing that was.

Then the Carnitor was stopped because the new fiscal intermediary would not cover costs where the previous one did. Within weeks, the RLS returned, and the episodes are already more frequent, lasting longer, and symptoms severe. The cardiac arrhythmias are also back and frightening.

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In conclusion, my quality of life was much improved on Carnitor and the outlook without it is bleak at best. Thank you for your attention.

MS. LONG: Thank you, Miss Hernandez. The next speaker is Edwin Scott.

MR. SCOTT: Good morning. I appreciate being here with you folks today. I came up from Georgia, and my expenses were paid by Sigma Tau due to my disability. I am a naval veteran, and I'm 59 years old and have been on dialysis going on six years, and been on levo-carnitine since April 27th of 2000.

A little history, I am diabetic, I have had open heart surgery, I have an atrial defib, and a few medical problems. But my doctor in April of 2000 said Mr. Scott, we're going to put you on carnitine. I said fine. That was the 27th. On the 28th I walked out after dialysis and went to a friend's business and walked out and fell down, and I took the palms off both my hands, I felt so good, and it has increased steadily. I have been on the drug 14 months. My leg muscles don't hurt, I don't cramp.

And in the packet I made to you folks

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today, there is an organ transplant letter from Piedmont Hospital showing an infraction of 25 percent, signed by Dr. Wetzel, and there is also a VA Medical Center report on the infraction of my left ventricle after levo-carnitine. One of them was in February, the other one was in July, I went on carnitine on the 27th of April, and the VA Medical Center medical report that is enclosed shows a left ventricle injection fraction of 36 percent. So just that one thing outside of my center, which I did personally, not my center, because my brother said, I'm going to give you a kidney buddy, I said okay, but he said this wasn't good enough to do it.

So here we stand. Carnitine has made

it so I can be here, I can take my father to his final resting place in February. Last year I couldn't climb stairs, but I climbed stairs today, here, at the hotel, wherever. These are things that increase our quality of life and our quality of life means a lot to us. We want to raise our grandkids, we want to see our brothers and sisters.

There has been a lot of talk about cost. Watching this presentation today, and I'm

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not reading today, I'm working from memory, but talking about costs, well, if we notice, most of the studies showed IV carnitine patients have less hospitalizations. Two years. So, you have 300,000 patients, 10 percent of them are well patients. If you take 60 days a year at an average of $1,000 a day in the hospital, and do the math. 30,000 patients, $60,000 a year with well patients comes up to a whole lot of money. It's not millions, it gets into the billions, and not even figuring what it costs for ICU care, which is three times the cost of just a regular room. And these graphs showed it today.

Enclosed in my thing was a little letter from another patient in Georgia. I have to get my glasses out, because this fellow here, I have to talk about him.

Mr. McDonald, who I met by phone, have not met personally, but Mr. McDonald, and this is a letter from his wife: First let me express mine and my husband's thanks for all your efforts on our behalf in securing Carnitor for his benefit. I would like to explain just a few of the details when receiving Carnitor, losing the benefit of Carnitor and receiving Carnitor for six doses as

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of today.

Mr. McDonald began dialysis in late 1996, first hemo, then PD. With PD he had lots of trouble, infection, double hernias, several

operations. After switching back to hemo he did fine for a while. His doctor put him on Carnitor, which helped his leg cramps and use of his muscles. He could walk, and we could go to the mall, and exercise three times a week. He was able to stand, preach in a small church for 15 minutes on Sunday, able to perform short funerals and other assistance, with assistance, which of course kept his self esteem up. He had preached for 40 years and his doctor felt that this small involvement kept him from being depressed. His health remained steady until 2000 when he was taken off Carnitor.

From that date until this month, he has steadily declined. He has had a heart attack, has given up any preaching, and any other assisted work, and it says work of any kind. He now cannot walk from the den to the mailbox at the end of the driveway, or from a chair to the bathroom down the hall, 40 feet. This of course has caused depression and his self esteem has deteriorated.

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Our retirement income is very limited and this has created another mental anguish problem for him since he cannot supplement the income, and it goes to say, the medical output increases.

With your efforts and Carnitor being returned during his treatments, he is now able to walk without assistance, his leg cramps are gone, he can breathe without the use of oxygen. His breathing had become so difficult that even eating he would have to stop halfway through and rest. At this point, he is sleeping on two pillows, but is able to breathe without difficulty. He could not shower and dress without taking two hours stopping for rest periods. However, now, only a slight shortness of breath is at completion.

Mr. McDonald's heart doctor now feels that his heart muscle is in shape enough that he has began mild cardiac rehab activities. His children cannot believe the difference in his stability, and have been able to take him out to

eat. After only these few treatments, and we're talking about two weeks, six treatments, the noticed difference is substantial. He is also able to speak over the phone to his family away from our state.

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Another surprise, last Saturday morning, he was able to stand up and actually cook grits and eggs for himself. To you this may not be anything special, but to us it's a miracle.

In other words, summing up, we believe in Carnitor. I only wish everyone who is on dialysis could receive it. Carnitine level does not always send the proper message. I can truly say to you, I believe I have my husband back from near death. And again, thank you. Mrs. Elvyn McDonald.

Folks, without this, there are many of us that will leave as my dad did in February, will leave this world. We need the drug to make this better for all of us. Your sister, your brother, your grandmother, think about how many people that you know, and everybody here has heard of somebody on dialysis. And we also need to get it in the VA system, got to get you on this one.

DR. HOLOHAN: We will get to that later.

MR. SCOTT: I'm just saying that from the patient standpoint, we feel that we're on the bottom of the chain and every time we start to get up just a little bit, they try to kick us down,

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including other drugs in our regimen. Thank you.

MS. LONG: Thank you, Mr. Scott. The next speaker is Dr. Joel Kopple, and following Dr. Kopple it will be Kris Robinson.

DR. KOPPLE: Hello. My name is Dr. Joel Kopple. I am a professor of medicine and public health at UCLA and also the head of the decision of nephrology and hypertension at Harbor UCLA Medical Center. I am here at the expense and

also the request of Sigma Tau. I sometimes speak for them, sometimes consult for them, and they have funded from time to time a number of my research projects. I have done a number of research studies on carnitine over the years.

Now, let's see if I can get this to work. I may need you back, or maybe you ought to stand next to me. You have a dinosaur before you, I apologize for that. Okay.

Now, as Dr. Chertow mentioned, I chaired the National Kidney Foundation K/DOQI clinical practice guidelines for nutrition in chronic renal failure. It's a longstanding several decade interest of mine, and I am here to talk a bit about the guidelines and also a bit about oral versus IV local carnitine.

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I should mention that I specifically appointed Glenn Chertow to oversee the development of the guideline on carnitine because Glenn is not only, as you can see, very bright and extremely expert in nephrology and medicine, but also because he has no conflict of interests whatsoever, and that was the reason why he developed this particular guideline within the work group and I stepped back for a bit.

Now, just a word about the guidelines, and I will try not to be too repetitive. First, we did use a classic, more or less a classic guideline development structured comprehensive review of the medical literature. We started with around roughly 24,000 titles and eventually, as in our experience, they ended up down to about 250 manuscripts which were carefully examined and rated.

We employed the Rand/UCLA appropriateness method, which follows the JAMA published guidelines for structure review and clinical guideline, practice guideline development, and also the, it used to be called the AHCPR, I think it's now called the AHQR, I think it is, or AHRQ.

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DR. HOLOHAN: AHRQ.

DR. KOPPLE: And it's staffed, and I apologize to Dr. Holohan for this, not only by the Rand Corporation, which as you know, Paul Chakel works at, but also by the West LA VA, which I actually worked at for 18 years.

DR. HOLOHAN: I read your CV.

DR. KOPPLE: It was actually maybe, probably the best time in my whole life was when I was there.

All decisions were made by private vote, and the guidelines were sent out sequentially to three different groups of people before they were finalized, first the K/DOQI, a very large steering committee which as Dr. Paganini has mentioned, is very multidisciplinary in itself and has representatives from organizations not only throughout the United States, but even some from outside this country. Then it went out to a large array of organizations, both within the nephrology and also the community, the nutrition community, both nephrology and nutrition organizations, as well as just general medical organizations. And finally it went out to roughly about 400

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interested participants, and these reviews were actually, comments were tabulated, critically analyzed, and then the final decisions were made about with the guideline development.

Now as you probably know, the guideline on carnitine reads as follows: There are insufficient data to support the routine use of L-carnitine for maintenance dialysis patients, and I would like to emphasize the word routine. I think the language was very carefully crafted and the word routine was put in there because it was clearly felt that obviously, it shouldn't be used for everybody. There is no evidence whatsoever that every dialysis patient should get it. But it

was on the other hand felt, the question in fact was left remaining as to whether it might be good for certain subsets of dialysis patients.

And there were two qualifying statements, which is very typical for most of our guidelines. The first was, and I read this, although the administration of L-carnitine may improve subjective symptoms such as malaise, muscle weakness, interdialytic cramps and hypotension, and quality of life in selected maintenance dialysis patients, the totality of

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evidence is insufficient to recommend its routine provision for any proposed clinical disorder without prior evaluation attempts at standard therapy.

Second, and last qualifying statement was, the most promising of proposed applications was in the treatment of erythropoietin resistant anemia.

Now just to summarize, this list contains what probably most people would consider potential indications for L-carnitine use, and they have been addressed earlier. These include malaise, asthenia, muscle weakness, decreased exercise capacity, intradialytic muscle cramps, intradialytic hypotension, impaired cardiac function, arrhythmias, low quality of life or in other words, a particularly poor sense of well being, erythropoietin resistant anemia, and hypertriglyceridemia.

I would actually like to congratulate and compliment Dr. Klassen, who I thought actually put together a very incisive and comprehensive examination of literature, but I do have to make one qualification, which is based on our own structured review and upon my own experience both

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with studying carnitine and with reading and examining the literature, and that is that it's really rather hard to compare these studies. And

particularly where it says there was not benefit versus there was a benefit.

For example, the Ahmad study which a number of people have referred to and which I was both one of the four principal investigators and also one of the architects of. Actually, and I think Dr. Klassen mentioned this, actually it evaluated arrhythmias and found no difference between placebo and a control group, and one of our problems in the study is it in fact was underpowered. We had a very very low incidence in both groups. Similarly, the incidence of hypertriglyceridemia in both groups at baseline was very small, so small that one would have predicted it would have been about four or six in each group, and it would have been impossible to show a difference even if carnitine does cause such a difference.

I think one needs to be careful in interpreting some of the negative studies, because sometimes there wasn't a high enough incidence of the outcome in question to, or excuse me, of the

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manifestation in question to adequately test it. And of course as Dr. Klassen also pointed out, a number of the outcomes were, number of the studies were in fact underpowered just by the small numbers of patients studied.

Now, every one of the guidelines has a rationale section in it, and the rationale section for the carnitine guideline included a brief overview of some of the research studies and some of the issues involved with trying to interpret the data. Nonetheless, it ended up with, this was one of the statements with which it ended, which reads, in selected individuals who manifest the above symptoms or disorders, and who have not responded adequately to standard therapies, a trial of L-carnitine may be considered in reaching these conclusions, because of the strength of evidence, of available evidence, as well as the alternative therapies available for each potential

indication. It should also be recognized that L-carnitine in fact, at least in my judgment, experience, as well as reading, in fact has a very safe adverse effects profile.

I must say that I was quite surprised at the strong association between seizures and the

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use of L-carnitine that Dr. Bonino has described. I must tell you, I was not aware of that, and I should point out that seizures are not uncommon, novo seizures and changes in the frequency of seizures are not uncommon in dialysis patients, and whether it's related to carnitine in her patients may well be the case. I must say that I just find this rather a striking association.

Now, the work group did not address the issue of oral versus IV carnitine, and I think it's fair to say that the reason that it didn't was because again, it felt the data was not substantial enough to really examine this question in detail, and -- but, what I'm going to say now is in fact --

DR. TUNIS: You have about 30 more seconds.

DR. KOPPLE: 30 more seconds. My personal opinion, that is that the bioavailability is small. Tests on bacterial flora are increased. There are logarithms greater, and they are in the small intestine in dialysis patients. So in fact, this is quite usual in normal, so they have the opportunity to actually degrade carnitine. There is evidence that some of the compounds that it may

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metabolize may be toxic in humans. And in fact conversely, carnitine in vitro may in fact promote proliferation.

This says many more trials; it should say including larger numbers of patients, probably more than just the number of trials, and this is my last slide, indicate potential benefits of IV carnitine than oral. That's my read of the

literature and experience.

And finally, oral carnitine may be as safe and effective as IV, but I would argue that we know less about it, and we don't have a good safety profile, and I'm not sure therefore, that it should be mandated.

Perhaps I will close, if I can, with one personal statement and that's my last slide. That is that I know if I was a maintenance dialysis patient and I had some of these multiplicity of symptoms these individuals has, and if I didn't respond to standard therapy, I would demand carnitine, not because I was certain it would help me, because it might help me, and I would demand it for my family for the same reason. And also because I think in fact it's safe, and because more is known about IV than oral, I would

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demand IV, and I thank you for your attention.

MS. LONG: Thank you, Dr. Kopple. Our next speaker is Kris Robinson, and following is Dr. Alexander Fleming.

MS. ROBINSON: Good morning. I'm Kris Robinson, I'm the executive director of the American Association of Kidney Patients and I am also a kidney transplant recipient. AAKP appreciates the opportunity to provide oral testimony to the Drugs, Biologics and Therapeutics Panel of the Medicare advisory committee today.

I would like you to know that we were invited here today by CMS, recently known as HCFA, and that none of my travel expenses have been covered by any company here represented. The American Association of Kidney Patients, also known as AAKP, is the voluntary patient organization which for over 30 years has been dedicated to helping renal patients and their families deal with the social, physical and emotional impact of kidney disease. As the only national kidney patient association directed by patients specifically for patients, we realize the important need to insure quality of care and

access to all dialysis, potential dialysis

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patients, and transplant recipients. Access to care for patients is a primary concern for AAKP and the patients we represent.

Though we do not have the expertise to be involved with reimbursement decisions and the cost of therapies, we do recognize that access to care must never be jeopardized for patients. Thus, there are several points which we wish to make to the panel today. Number one, AAKP is concerned that the differences in each intermediary's reimbursement policy results in a situation where some dialysis patients have access to drug reimbursement and the medicines their doctors prescribe while others do not. The inconsistencies across the United States leave patients confused at the very least, and lacking coverage that exists for others at the very most. It is our belief that when medication or treatment is approved by coverage by certain intermediaries, it should be reimbursed by all to allow for an even playing field amongst patient care.

Point number two, AAKP is concerned about how physician prescriptions may be altered due to inconsistent policies. Dialysis facilities, as you may know, use different

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intermediaries for billing. Thus, though a patient may receive a prescription from his physician for a medication and receive it in his unit because it is Medicare reimbursable through that intermediary, that same patient may travel for business or pleasure, and find that he cannot receive his medication in another area due to an intermediary's decision. Thus, if the patient is not able to pay for the drug himself or through a secondary policy, the prescribed medication that he has been receiving at his home unit is denied. This is in direct conflict with the doctor's prescription.

Point number three. The patchwork nature of the current process can discriminate according to geographical location, again because dialysis facilities use different intermediaries for billing, a patient dialyzing in one part of town may be able to receive prescribed medication reimbursed by Medicare, while another patient dialyzing at a unit across town may not. Without a consistent national policy, we worry that access could prevent a segment of the population from securing services.

AAKP commends the panel for addressing

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the issues of access to medications and therapies for ESRD patients. We appreciate the opportunity to provide you with input into your efforts and encourage you to assure that today's outcome will provide for consistent access to Medicare benefits for all patients. Thank you.

MS. LONG: Thank you. Our next speaker is Dr. Alexander Fleming.

DR. FLEMING: Thank you very much, Mr. Chairman. In my capacity as the chief scientific officer of a contract research organization, I have occasionally provided Sigma Tau consultation services, and Sigma Tau has compensated me for appearing here today.

I think my role here is to comment on the FDA approval process in general as it pertains to the review of Carnitor or L-carnitine. I left the Agency three years ago after 16 years of service in the public health service, first at NIH and then for 12 years at FDA. When I left the Agency I was senior endocrinologist. I do acknowledge Dr. Klassen's important point that FDA approval is necessary but not in itself sufficient for authorizing Medicare coverage for an approved therapy, but I would also add that the FDA review

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process integrates a wide number of considerations; it's what we might consider as

where the rubber meets the road in terms of the interface between clinical practice, scientific evaluation and public policy.

Just a quick review of the general principles of FDA therapeutic process, and for probably most of you, this is not really necessary. But I think it's well understood that generally two well controlled studies are required to provide substantial evidence and substantial evidence is an important concept here. A specific therapeutic benefit needs to be identified, and the Agency has to assess whether the benefit to risk relationship for the proposed treatment is acceptable for the proposed clinical indication. Ultimately, the task is to determine if a therapy is safe and effective for the intended use, based, on a review again, of substantial evidence.

FDA's considerations in determining what constitutes substantial evidence is probably relevant to the deliberations today. As you can understand, the size of the targeted patient population is certainly relevant. When large numbers of patients are available for clinical

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trials, it makes it easier to conduct robust studies, and that is the theory behind orphan drug considerations. These therapies are certainly important when any unmet medical need exists, and there is a greater priority to fill that need.

Ethical considerations are certainly important in what can and cannot be answered with clinical studies, and I think we ought to come back to that point as it pertains to the comparison of oral carnitine and intravenous carnitine.

Finally, the kinds of outcomes that can reasonably be measured in the real world have to be considered. And there are many other considerations, but I think those are enough for now.

Let's talk about the FDA's considerations in determining how effectiveness

should be measured. First of all, there is the issue of what kinds of outcomes should be measured and we will drill down on that in a moment. Then there is the issue of what kind of magnitude of response would be considered clinically meaningful, and of course that is a human judgment. Then there is the issue of whether

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there is the need to demonstrate an ultimate clinical outcome and if so, when, in relationship to approval of the therapy. Finally, there is often the challenge of balancing the competing priorities of reaping scientific conclusiveness and providing for unmet patient needs.

Now, just a few words about surrogates in therapeutic development and regulation, because that is of course very pertinent to today's discussion. Surrogates in this context are outcomes that are deemed very likely to reflect but not actually represent in themselves clinical benefits. Obviously, surrogates have had very important roles in the approval of therapies for many chronic diseases. I think all of you are aware of the stores of the lipidfluorine therapies, therapies for diabetes and hypertension as being good examples here. The concept of surrogates in therapeutic regulation is well established in FDA lore, and more recently has been codified in law with the FDA Modernization Act of 1997 being an example.

And I might just mention that the distinction between a clinical outcome and a surrogate outcome is not always clear. And as an

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example, I would point out that blood glucose is a surrogate for diabetic complications, but also it is a clinical parameter in itself that is directly related to symptoms and metabolic derangement that requires immediate treatment. And by the way, the surrogate, glucose as a surrogate for diabetic complications has taken 40 years to confirm, but

in the landmark studies reported in the past five years have actually shown that relationship. So what this comes down to is that any given therapeutic indication has a wide spectrum of possible outcomes for supporting it at the regulatory review level.

What about FDA options when a surrogate outcome is the basis of an approval? First of all, for the past eight years there has been something called the accelerated approval mechanism, which actually makes it possible to provide a conditional NDA approval. The effect of this is that a therapy can be approved but a confirmatory study of the clinical benefits is required and must be recorded within a stated period of time. The therapy can be, or the approval can be withdrawn if the results of the study are not confirmatory or if the data

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themselves are not forthcoming.

The FDA may also, and frequently does place requirements on the sponsor for conducting post-approval studies, and this is seen very commonly with therapies of all sorts and involving populations of all sizes. And finally of course, the FDA has the option of not requiring any further studies at all.

And going back to Dr. Tunis's question I think early on about grading the kinds of situations that may be encountered, we could consider these perhaps grade A, B and C.

Key facts in the review of carnitine that are available in the public record and which I have had reviewed are simply summarized here. First of all, and all this has been well presented, I won't go into detail, but obviously hemodialysis clearly removes carnitine from the blood. Patients with end stage renal disease on hemodialysis have or are at risk for carnitine deficiency. Parenteral carnitine supplementation comes down to being the only practical means for repleting the deficiency state resulting from

dialysis, and manifestations of carnitine deficiency have been well described in patients

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with the condition for which carnitine was previously approved.

Important observations that are actually documented in the FDA review include the fact that carnitine deficiency can lead to serious and life threatening conditions, as observed in other disease studies where carnitine is deficient. Again, dialysis patients were acknowledged as suffering from carnitine deficiency, and they have frequently a clinical picture resembling the syndrome that has been observed in patients with other carnitine deficiencies.

IV carnitine was clearly efficacious in raising carnitine levels, and that was ultimately the basis for approval by the FDA. Furthermore, they looked at the meta-analysis of controlled trials and other studies and decided that there was a sense of clinical effectiveness, though these studies cannot by themselves be considered definitive. The probability ultimately appeared high, and they documented this in their review, that dialysis patients would clinically benefit from carnitine supplementation.

Improvements in the clinical status of

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exercise tolerance were not shown and this was pointed out in the review and it was insisted that this be reflected in the drug product label. However, the significance of this stipulation should be understood. This was a way of informing the prescribing physicians about the nature of the data on which the approval was based. It was not to indicate that the FDA approval was based on less than substantial evidence or the clinical benefit should not be expected from carnitine therapy.

Ultimately, the FDA agreed --

DR. HOLOHAN: Dr. Fleming, I'm going to ask you to try to wrap it up.
DR. FLEMING: This is my last slide.
DR. HOLOHAN: You are significantly over time.
DR. FLEMING: The FDA did obviously approve the therapy and did so on the basis of pivotal NDA studies that were statistically powered to biochemical outcome, but were not powered to demonstrate clinical benefits. Importantly, additional trials to substantiate the clinical benefits could not be justified in the eyes of the FDA and that probably deserves further

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discussion.
Thank you, and I apologize for running over.
MS. LONG: Thank you. Our final speaker is Vyoone Lewis.
DR. LEWIS: Good afternoon. My name is Dr. Vyoone Lewis, and I am executive director of Renal Beginnings, which is an organization designed by Early Intervention and Education Services to minority populations at risk for chronic kidney disease. I do serve as a medical consultant with Sigma Tau Pharmaceuticals, but the data I will be presenting this afternoon is on behalf of Dr. James Bazemore, who is the president of the Georgia Society of Nephrology, and Dr. Stephanie Woollen, both of whom have no financial interest with Sigma Tau Pharmaceuticals.
I was asked to come today on their behalf to present data that in the spring of 2000, patients at their dialysis centers who had been previously treated with IV carnitine had to discontinue therapy because of the negative coverage decision by Blue Cross/Blue Shield of Georgia. They took this unfortunate opportunity to study the effect of that withdrawal on health

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of such patients, and this was a very unique

opportunity in that a lot of the studies that you've heard about today really have not looked at the effect of carnitine therapy once it was discontinued in those patients throughout those studies. And I will go through these slides for Dr. Bazemore and Dr. Woollen.

It was a retrospective observational analysis. 35 patients were included in the review and they looked at the patients data six month prior to the patients being on IV levo-carnitine, six months of levo-carnitine supplementation, and then six months following discontinuation of IV levo-carnitine therapy.

This is the demographic data. The total patients reviewed were 35, there were 20 females. There mean age was about 53.5 years. They were on dialysis for about 1.5 years. Mean URR was 67. The mean length of time on dialysis was 9.3 months, and the average carnitine dose was 1.5 grams of IV following each hemodialysis session.

The type of dialyzer were F-80s, and this was also interesting from some of the other studies that we have seen today in that these

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patients in this review were actually included because they were picked for an indication for carnitine therapy similar to what we saw in Dr. Lindberg's data.

The rationale for IV carnitine therapy in 20 of the patients was what they call cardiomyopathy, which was not responsive to standard therapies. Now there was an interesting question about defining cardiomyopathy earlier, and that was my question to Dr. Bazemore and Dr. Woollen, what do you mean when you say cardiomyopathy? And it really means in a nephrologist's mind any patient that has a congestive heart failure, dialysis induced hypotension, and arrhythmia. So those were patients who were included in this review that they had had on other conventional therapies that

were not responding appropriately, and it was there method of sort of a search to look at some other alternative therapy to help and manage these patients.

They also had eight patients that they had on therapy that were hyporesponsive to epogen that were on high doses of epogen that were not responding in terms of improvement of hemoglobin

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hematocrit values, and seven patients that had just severe malnutrition that was just doing poorly, low energy levels that they wanted to see if this therapy would help.

What they did was they used a paired student T test and they looked at some parameters at the time periods set out. Earlier, they looked at ejection fractions, they measured frequency of hypotensive episodes, they looked at serum albumin, hematocrit and ferritin levels, epogen dosage, and also the patient's perception of their functional capacity.

I am going to go through each one. This is actually the ejection fraction data and this shows the group mean ejection fraction, there was only 7 of the 20 patients that had actually had echocardiograms done and had ejection fractions, but the baseline, the rate here represents what their baseline ejection fractions were prior to therapy, and then the green line represents six months following IV levo-carnitine therapy. And their mean ejection fractions prior to baseline were about 17.5 percent with a standard deviation of about 2.5. And we see after six months of IV levo-carnitine, their ejection

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fraction has significantly increased to 30 percent, with a standard deviation of 40, and a p value of .001.

And that's the group mean, but if we actually look at the individual ejection fractions individually -- I mean, I thought about Mr. Scott

as I present this data, because this is Mr. Scott, I mean, his ejection fractions goes from a low of 15 to a high of 30, and this is a difference between a patient that has a severe cardiac compromise, a patient who has severe congestive heart failure, and you're improving that patient's cardiac status.

When we look at the group mean number of hypotensive episodes, these were monthly values. Baseline, the hypotensive episodes were about 12.2. After six months of IV levo-carnitine, their hypotensive episodes were as low as 4.5, and Drs. Bazemore and Woollen have indicated that this therapy really has helped in improving dialysis runs with these patients. I don't know if you know what it means for a patient to have a hypotensive episode when they are on dialysis, but it's very painful, it interrupts the treatment, you cannot adequately dialyze them, so

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you don't accomplish your goal of dialysis and it's really very difficult. So this has meant a lot in their clinics in terms of being able to adequately dialyze their patients and reach their treatment goals.

And we see after the carnitine was discontinued for six months, those hypotensive episode once again went up in those patients. And I suspect these are probably those severely cardiac compromised patients; those are the patients that are more prone to these frequent hypotensive episodes. We know that these episodes are multifactorial. As we've heard, they can be related to fluid overload, a lot of problems, but there are some episodes that can be helped with carnitine therapy.

When you look at the data, all 20 patients the initiated therapy secondary to what she called refractive cardiomyopathy, which I learned is the patients with congestive heart failure, hypotensive episodes and arrhythmias, nephrologists have unique ways of defining things,

they had a significant improvement in frequency of hypotensive episodes with a p value of .001. And once the IV levo-carnitine was discontinued, they

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saw a significant in hypotensive episodes with a p value of .005, and these patients were the patients that actually reported an improved sense of well being related to their functional capacity when they were receiving IV levo-carnitine therapy.

These are the category of seven patients that they had that were hyporesponsive to epogen therapy, and they defined hyporesponsive as patients that were on 10,000 or more units, and there were seven patients that they put on carnitine therapy for this reason, and actually there was a very heterogeneous response with these patients. When you look at the seven patients, only about four of the seven actually had a significant decrease in epogen therapy when they were on carnitine therapy, as well as the improvement in hematocrit values which you will see in the next slide. The blue represents the baseline, and the purple was after six months, and then the yellow is the discontinuation of therapy.

And this was that group's mean hematocrit values, the hematocrit values at baseline were about 35.4, they had improved to a level of 37.1 after six months of carnitine

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therapy, and then they went back down to about 35 once the carnitine therapy was discontinued.

So in four of those seven patients, there was actually a 30 to 50 percent reduction in epogen dosage with normal iron status. Improvements in hematocrit values were seen in these patients despite decreased epogen dosage and stable iron supplementation. And once the therapy was discontinued, a significant decrease in hematocrit levels and increase in epogen dosage was noted.

Now I know some of the scientific experts earlier mentioned that there are multifactorial reasons why these patients are hyporesponsive to epogen, so its always good to rule out before you put the patients on carnitine some of those other reasons, and I think that's the approach that Dr. Woollen has taken in this data set, and I think that's why she's terming it refractory cardiomyopathy.

She also looked in the patients that she put on for malnutrition, she looked at serum albumin levels, and I know there is a lot of controversy now in the nephrology community about albumin as an indicator of malnutrition, because

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it is also a marker of inflammation in those patients. But this is the marker that she used to monitor if the patients were improving in terms of their malnutrition status while they were taking IV carnitine therapy. And what she found was the green is the before, after six months, and then after discontinuation. There were really no changes in albumin levels, it didn't have any effect on albumin levels at all in any of those patients, so there was no significant change in serum albumin during or following IV levo-carnitine therapy.

So I think, when I think of Dr. Woollen, Dr. Kadree mentioned earlier that the experts in nephrology know how to pick patients, the subset of patients that will benefit from this therapy, and I don't think this person, she's this country doctor in Georgia is what I think of, and I think if we can develop a prudent policy that would help the nephrologists identify which subset of patients would benefit, what are the interventions that we should rule out before putting those patients on therapy, then we can select those patients that would appropriately benefit.

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And I do want to make one other comment to Dr. Kadree's and Dr. Bonino's data on cost utilization, since we seem to keep coming back to costs. A lot of that data was collected prior to 1999, and this product has been indicated since December of 1999, and as a result of that, there has been a huge, and I know because I am an ex-renal dietician, I have been out there in the community, there has been a huge lack of education about the use of this product in dialysis patients, and not because of Sigma Tau not wanting to educate the dialysis providers, because they couldn't because it was not indicated.

But I think now that there is an indication, if this committee can come together and put together a prudent policy, that we should be able to identify those patients who would benefit from therapy. And I thank you for your time and attention.

MS. LONG: Thank you. We will now break for lunch. We would like to try and do it for 45 minutes, if that's possible. So according to my watch, 45 minutes would be about five after, possibly ten after.

DR. HOLOHAN: Ten after.

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MS. LONG: Okay, ten after. Thank you.

(Luncheon recess from 12:26 p.m. to 1:30 p.m.)

DR. HOLOHAN: Thank you, Sean. In discussion with HCFA personnel prior to the meeting, we had concluded that there would be two reviewers, primary and secondary, but the primary and secondary were never specified, of the evidence. Cathleen Dooley and myself were, how shall I say, suggested and nominated by the members of the panel. There were only two dissenting votes.

But in any event, we are going to try to do a short summary of the data that we had available, made available to us by the Health Care Financing Administration. Some of this may be a

little repetitious from some of the presentations earlier this morning. I will try to be concise and precise and emphasize some slightly different issues.

I presume, I know the panel, I don't know if the audience has the evidence charts, evidence tables that I put together. My indications are a little bit different than those on the evidence tables used by the Health Care

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Financing Administration. Some studies are repeated, because a number of the published studies had multiple outcome measures. I will make some comments during the mention of a few of these published papers of what I believe to be some problems with the study or the protocol as reported.

I presume the panel has in front of them these evidence tables. I am not going to go through these study by study, but there will be a summary at the bottom of each chart and I will mention a few issues that haven't been emphasized so far by either HCFA or some of the proponents or some of the people who have questioned the use of carnitine IV.

The first table is entitled Effect of Exogenous L-C Upon Exercise Capacity and Strength. I decided to combine exercise capacity and strength, since the studies were fairly few, I think there are only seven. Ahmad has been cited a number of times, and this was a multicenter randomized control trial. I should tell Cathy, I use the words randomized if there was any randomization at the beginning. The only other categories I included were crossovers and case

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series. So randomized control trial is used in its broadest sense.

In Ahmad's study on maximum O2 consumption, they only measured this in 37 of the 82 patients, and it was only measured at three of

four centers, so this measure was not uniformly made across all 82 patients in the four centers involved. They measured exercise capacity by maximum O2 consumption using a bicycle ergometer, and the load was increased until patients couldn't maintain a 50 RPM baseline. So it was essentially exercise to max capacity or exhaustion.

The results according to the authors were that levo-carnitine, which was given in the dosage indicated, resulted in an increase in max O2 consumption. However, the magnitude of the increase was from 1,140 to 1,250 milliliters per minute, and that's corrected for body weight, and I will leave it to the panelists to determine if the difference between 1,140 and 1,250 is clinically significant.

Brass did a similar study. This was a two-part randomized control trial, and the protocol called for two separate groups of people and the patients randomized to L-C in each of

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those, Studies A and B, got different dosages of L-carnitine. One was 60 milligrams per kilogram per week IV, based on three dialyses, and the second study actually used a dose escalation, three different dosages. They also used a bicycle ergometer and they found no difference between levo-carnitine and the placebo in either Study A or Study B.

What they did though, was to do a secondary analysis where they combined Studies A and B and showed a small positive effect. They said they used a mixed linear model adjusting for baseline data and dry weight. The placebo showed a slight decrease in max O2 consumption, the levo-carnitine showed no decrease, and this is what they describe as a small positive effect. Again, the difference was 56 milliliters of oxygen per minute. And again, I will leave it to the panel to determine if 56 is a significant difference compared to baselines of 1,250 to 1,400.

There's something more important in this, though, and this was something that appeared in a number of other studies, and that was a post hoc analysis after completion of the protocol.

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Let me read a comment from Tricia Greenwald, who wrote a series of papers published in the British Medical Journal on statistics for the nonstatisticians, which I guess fit most of us here. And one of the things she talked about was looking at a study to see if the data were analyzed according to the original protocol. I'm going to take a few minutes, or few seconds, to quote exactly what she said.

"If you play coin toss with someone, no matter how far you fall behind, there will still come a time when you are one ahead. Most people would agree that to stop the game then would not be a fair way to play. So it is with research. If you make it inevitable that you will eventually get an apparently positive result, you will also make it inevitable that you will be misleading yourself about the justice of your case.

"Raking over your data for 'interesting results', retrospective subgroup analysis can lead to false conclusions. In an early stud on the use of aspirin in preventing stroke, the result showed a significant effect in both sexes combined. A retrospective subgroup analysis seemed to show the effect was confined to men. This conclusion lead

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to aspirin being withheld from women for many years until the results of other studies showed that the subgroup effect was spurious."

People who are into methodology can find many other reviews and commentary similar that talk about the danger of what I guess most people in medicine call data dredging, retrospective post hoc analyses. I won't go through all of these in detail.

Bellinghieri used PO IV carnitine,

tested knee flexion, three-step climbing, after and between analysis, and they assessed fatigue by the time it took and the number of steps a patient could achieve, and they presented the results graphically, so it was kind of hard to get magnitudes, but it appeared that the post-dialysis fatigue measures decreased approximately 2.5 down to .25 on a one-to-three scale, and the authors concluded that was a dramatic fall in those symptoms.

Fagher used knee torque with a dynamometer and found no significant difference.

Giovenali used maximum voluntary isometric quad contraction, a reference to methodology they used, but they didn't specify

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exactly how they did the study, and found significant increase in force values for two of their three groups; those two groups were on intravenous as opposed to PO L-carnitine. But it only occurred in seven patients out of 16. This is something we're going to see repetitively, that even where an overall group analysis showed significant difference, it may have been restricted to some of the patients, almost all the benefit occurred in some of the patients an another fraction showed absolutely no benefit.

Siami measured overall activity on an interview scale that ranged from normal activities of daily life to bed bound. The placebo group went from an average score of 3.5 to 3.1, slight improvement; the carnitine group from 3.4 to 2, it wasn't statistically significant, but the authors also claimed a cluster of responders, again, after completing the study, so this was also a post hoc analysis.

In summary, for these studies, there were five randomized control trials, one crossover, one case series. Four studies showed no difference in exercise capacity and strength, and three showed improvement. Of the three

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showing improvement, two used the intravenous dose form, and one oral dose form.

Regarding cholesterol, triglyceride and HDL levels, we've been told by an earlier speaker to ignore all this, but in fact, this is the most common set of outcome measures that appear in all of the literature provided by HCFA, so although we are told to ignore it, apparently the researchers did not.

I won't go through these piece by piece, but in this series, there were six randomized control trials, ten case series, one crossover, one control group that was not randomized or at least apparently not assigned in a random fashion, and one study that used as a control group predialysis patients, and one could argue I think convincingly that a patient who's predialysis is not intrinsically medically comparable to a patient who is on dialysis.

No studies showed changes in cholesterol. With regard to triglycerides, four reported a decrease, one an increase, two an increase only in the phase off levo-carnitine, nine described no change. Decreases in triglycerides occurred both with PO and with IV

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use.

For high density lipoproteins, three studies reported an increase, which is good, ten no change, and the increase occurred both in PO and in IV administration.

There are some additional things to remark on. In the first study, Bellinghiere, all the patients had triglyceride levels at the beginning that were less than 230, which is really not hypertriglyceride anemia by most clinical criteria. Elisaf, who said that triglyceride levels decreased with IV use, the average triglyceride level went from 225 to 211, which is not clinically significant; both are slightly above the normal range. Similarly, for Lacour's

study, the triglyceride decrease was fairly modest. And in Vacha's study, a case series of 29 patients, there was probably quite a significant decrease, from 350 to 150, but it appeared only to occur in 12 of the 29 patients who started with low HDL levels.

So again, the benefits on cholesterol, triglyceride and HDL levels are inconsistent.

In terms of effects upon hemoglobin hematocrit and red cell counts, which were

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measured variably by different investigators, there were five randomized control trials, one controlled trial with a control arm that wasn't clear that they were in fact randomly assigned, two crossover, one case series. For hemoglobin levels, one study showed an increase on levo-carnitine, four no change. For hematocrit, three showed an increase, three no change. And for red cell count, one showed an increase, two no change.

In terms of cardiac dysfunction, which we've heard a fair amount earlier, the studies that I found among those forwarded to me by HCFA used as a measure arrhythmias, dyseneia on exertion, ventricular or supraventricular premature beats, and an ejection fraction the day after dialysis. The measurement tools were respectively a Holter EKG, patient reports of dyseneia after 10, 20 and a 30-step climb and what the authors describe as strolling for 100 and 500 meters. Suzuki used continuous EKG during dialysis, and van Es who measured the ejection fraction, didn't specify the technique they used; my presumption was since it was 1992, they probably used ultrasound measures of ejection

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fraction.

Two of the four studies showed an improvement in these measures. Both of those, Casciani and Suzuki, administered L-carnitine by

mouth. Van Es's study in again, a post hoc subgroup analysis, determined that ejection fraction had increased in seven patients who were symptomatic, which they defined as hypotension in dialysis, but not in six asymptomatic patients. Their initial protocol for this study didn't prespecify whether patients would be evaluated on the basis of hypotensive symptoms during dialysis.

I found only three studies on the erythropoietin requirements, Kletzmayer, Labonia and Semeniuk. All of these used intravenous formulation. Two were randomized control trial, Semeniuk's was a crossover study. The dosage varied. Kletzmayer found that there was a mean decrease in erythropoietin requirements of 36 percent, but it occurred in only eight of 19 of the experimental group patients; in other words, the 36 percent average decrease was totally due to dramatic decreases in a little fewer than half of the experimental group patients.

The authors concluded from this that a

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disturbance of levo-carnitine metabolism is not simply a deficiency that can be restored necessarily with supplementation; they didn't provide further explanation. Similarly in Labonia's study, the mean decrease of 38 percent, very very similar to that reported by Kletzmayer, was really a result of the decrease in seven of the 13 experimental group patients, again indicating that there may be some subgroup effects which really should be addressed in a follow-up study.

What I used as quality of life were only the studies that used an available reliable and validated measure such as the kidney dialysis questionnaire or the Short Form 36. One was a small study of 16 cases and the other was 101-patient randomized control trial. Sloan, we have had referred to before; they reported an improved general health and physical function which is two of the eight SF-36 scales, but that

was not sustained for the duration of the study.
And finally, the effect of exogenous levo-carnitine upon symptoms, there are a fair number of studies. I will limit my comments to the fact that Ahmad's study, for example, reported

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improvement in symptoms but they reported it by patient numbers, so if the patient reported an improvement in symptoms, the magnitude of that improvement wasn't counted, the patient was counted as a yes. So it was basically an all or none test, patient either reported improvement in symptoms or did not report improvement in symptoms, the order of magnitude of that improvement was not assessed.
And they concluded that asthenia decreased, hypotension decreased and cramps decreased, all were significantly different from the placebo. Brass's study had a statistically significant improvement in fatigue, none of the other measures, but on a Leichert scale of seven to one where seven is asymptomatic and one is severe, the improvement in fatigue went up by .05 out of a scale of zero to seven. The exercise testing from Brass, we've already talked about. Casciani looked at symptoms, and curiously, they said they monitored 11 symptom but they only told about four, which were asthenia, cramps, hypotension, and dyseneia on exertion. These were assessed by patient interviews every two weeks, and their conclusion was that there were no

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differences between the levo-carnitine and the placebo arms. We don't know what the other seven symptoms that they didn't monitor were.
In sum, in these studies there were four randomized trials, two crossovers, one case series. Four of the studies showed improvement, two used the IV formulation, two used the oral formulation. And three studies showed no difference between levo-carnitine and placebo on

symptoms; all of those three studies used the IV formulation. I am finished.

MS. DOOLEY: As Dr. Holohan mentioned, I am the second reviewer and what I'm going to do is just basically go through and look at the questions that HCFA asked us. The question posed to the panel was whether there was adequate evidence that carnitine deficiencies associated with the clinical outcomes in patients with ESRD on hemodialysis.

We were provided 36 articles by HCFA as well as a significant amount of information that was submitted by the manufacturer Sigma Tau. Most of the articles and information related to clinical outcomes and although the evidence is somewhat limited, it appeared that sufficient

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evidence had been provided to permit a conclusion that carnitine deficiency is associated with clinical outcomes in patients with ESRD on hemodialysis.

We were asked whether there was adequate evidence that the administration of L-carnitine was effective as a therapy to improve clinical outcomes in patients with ESRD. We were advised to consider the evidence both in aggregate as well as specific clinical conditions such as anemia management, cardiac dysfunction, disorders of muscle strength, and physical functioning or exercise capacity. As noted, there are some limitations associated with many of the studies of L-carnitine, and many examples this morning have been cited as why those limitations might exist.

For example, many sample sizes were small, the duration of the studies were variable, and the focus was also on subjective symptoms which are difficult to evaluate in an unbiased manner. Dr. Holohan and others have described the studies in detail so I won't duplicate that information. I think the DOQI opinion that there is insufficient data to support the routine use of L-carnitine for maintenance in dialysis patients

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has probably been demonstrated. However, I think there is an overall impression of the studies that when you consider them as a whole, they suggest that certain dialysis patients who have not responded to standard therapy can have improved outcomes when treated with L-carnitine.

We were asked whether there was adequate evidence that the effectiveness of L-carnitine is different from IV administration compared with oral administration, and I think there are two issues that need to be addressed on this. In light of the studies which form the basis of the FDA approval of IV L-carnitine in patients on dialysis, there is no question that IV administration is effective in raising L-carnitine levels. Also, IV administration has proven to be safe at fairly high doses and there are no warnings or contraindications listed in the PI.

Second, it's my opinion that there is inadequate evidence regarding the safety and efficacy of the oral administration and furthermore, the manufacturer noted in its submission that the long-term exposure to oral L-carnitine can lead to the accumulation of a potential precarcinogen in patients with renal

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impairment. Although this risk is theoretical, it should not be overlooked, especially in light of the availability of an FDA approved IV formulation.

I am sure like many of you, we have seen L-carnitine advertised in dietary supplements, but I think one thing to make sure we note is that the issue before us is L-carnitine approval as a drug. Both FDA and HCFA have definitions of drugs, and for Medicare the definition of a drug is specified in the Social Security Act. The key point that L-carnitine is listed in the USP and therefore qualifies as a drug for both FDA and Medicare purposes.

There is additional information that I think is pertinent to our deliberations that need to be brought to the panel's attention, and the first of that relates to the FDA review process and the use of the surrogate end point for the approval of L-carnitine. This slide summarizes the FDA's traditional standard for approval of new drugs. And the Federal Food Drug and Cosmetic Act requires substantial evidence of the effect that it is claimed to have based on the information presented in well controlled studies, that the

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current conditions described.

I think most carrier and intermediary medical directors are familiar with this standard, and they generally rely on the FDA label as an indication that a particular drug is safe and effective, and therefore eligible for Medicare coverage. However, in the case of L-carnitine, there is a statement on the label that causes concern and obviously has been the focus of some discussion.

The specific statement in the FDA label which reads, the effects of supplemental carnitine on the signs and symptoms of carnitine deficiency and on clinical outcomes in this population have not been determined. Clearly, if you took at that statement alone, it raises serious questions in the context of Medicare coverage and I can see how some carrier and intermediary medical directors when they reviewed this statement, they could conclude that there is no basis for coverage under Medicare, because the effects of carnitine have not been determined. But I think when we look at this we need to also look at it in the context of the FDA review process.

The FDA reviewed the clinical data and

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information that was presented to it by the manufactured and in the case of L-carnitine, that did include two placebo controlled studies which

have been reviewed this morning. The FDA does not conduct independent review of the medical literature as a routine part of their drug application review process and consequently this statement in the FDA label cannot be interpreted to mean there's no evidence of L-carnitine clinical effectiveness.

If we look at how the FDA concluded the effects of supplemental carnitine on the signs and symptoms of carnitine deficiency and on clinical outcomes in this population, how that was determined and how the approval was made, I think it was noted this morning that FDA's approval is based on surrogate end points of L-carnitine, and I think people are familiar with the fact that the FDA, and as noted in the FDA review material that we received in the panel, that there was ample evidence that carnitine deficiency can be a serious life-threatening condition, there is ample evidence that hemodialysis depletes carnitine stores, and in light of the safety of carnitine, efficacy in the treatment of carnitine deficiency

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may be inferred from the data showing that carnitine levels are maintained or actually increased.

This statement is included in the FDA guidance documents and was cited in material from the manufacturer that was provided to us by HCFA, and I think what it says is that FDA can accept a surrogate end point in the absence of the data on mortality and morbidity which is traditionally accepted with a new drug application.

I think one thing to note, and someone noted this earlier, that L-carnitine is considered an orphan drug, and I think people are familiar with the Orphan Drug Act that was signed in 1983. It's again not intended for routine use, but there may be a certain defined patient population from the studies that we saw that actually do benefit from the treatment with L-carnitine.

Another point of background information

I think we have to consider as we begin our deliberations regarding Medicare coverage is the coverage for drugs and biologics as outlined in the Medicare coverage manual. Obviously this is a longstanding policy, and I think the key phrase is actually bolded, specifically, FDA approved drugs

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are considered safe and effective when used for indications specified in the labeling, for drugs' safety and efficacy are longstanding criteria that are used to determine whether or not an item of service is reasonable and necessary and therefore covered under Medicare.

As HCFA has revised its coverage decisions over the past several years, the criteria for determining whether an item or service is reasonable and necessary have been in evolution and in light of this longstanding coverage policy, we have to have a discussion and understand what would make this a reasonable and necessary coverage decision.

The last issue that I think has to be raised is the existing Medicare policy that has a direct bearing on our deliberations, because L-carnitine is available both in oral and parenteral administration. If you look at the slide, and this is from the Medicare carriers manual, it says medication given by injection is not covered if standard medical practice indicates the administration of the medication by mouth is effective and is the accepted or preferred method of administration. Under this policy, injectable

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drugs are not covered if the oral route is accepted or the preferred method of administration.

In addition to the studies we have available for our review, I think we also have to take into account this current policy and consider whether oral L-carnitine is the accepted or preferred method of administration, and I think

that from the information we saw this morning, obviously the safety and efficacy was demonstrated in IV. Thank you for your time.

DR. TUNIS: Okay. We have temporarily lost our chair, but we will move on to the part of the agenda which is an opportunity for open public comments at this point. Could I see just by a show of hands how many individuals would like an opportunity to address the panel during the open public comment period? So, each of these individuals could have about three to four minutes of time in this open comment period, and why don't we start over here, with the gentleman in the back and if you would, restate your name and your affiliation, although I think the folks here know who you are, but for the purposes of the record, please restate your name and affiliation.

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MR. SCOTT: Mr. Edwin Scott, from Villa Rica, Georgia, a long way away from here, here at Sigma Tau's beckoning, and they have helped with the expenses.

My feeling is that we're looking at a population of roughly 300 million people in this country and we are talking about 300,000. And of these 300,000, we're not saying 300,000 need the drug, and nobody has stated that today. We're stating that there are people like myself who exceed the drug, Mrs. Hernandez, who the drug has helped her, Mr. McDonald, who is back on the drug for two weeks and can cook his own breakfast, doesn't sound like a whole lot. But to us, I just walked to a restaurant, probably two blocks and two blocks back. That's a big thing for us, by being able to get up and go.

We spend millions and millions of dollars on all the other millions of people that are HIV positive and everything, but we are talking about a very little segment of this population. As I said before, every time we get our head up over the wall, we seem to get kicked in the head and have to get knocked back down.

This would help. It helps me, it helps other

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people. We don't want a blanket coverage, we just want our nephrologist to be able to say, go through our records and say you're qualified, we're going to try this for six months; if it does good, fine, we'll keep you on it, but if it doesn't, okay. But we don't need to make a regulation so strict that it makes the provider, our dialysis companies shy away from it.

It was enumerated here by Dr. Kadree that they are what we call hooking in the patient class, medical review, every Carnitor claim. No. Why should we all be hooked if it's doing us good? If our nephrologist is not qualified to be a doctor and figure out what's best for their patients, they are not doing their job. They don't need to have somebody over at HMO, sorry, you can't do that. Who's making the decisions? We're here to make a decision today for several though patients in the country who need to be so situated as I am. I thank you for your time.

DR. TUNIS: Thank you, sir. Do you want to go next?

DR. SCHREIBER: I am Dr. Brian Schreiber, Fox Valley Nephrology Partners. I did want to be able to present at least one of the

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algorithms and discuss it. I have my disk here but there's probably not time to bring it out. I know that copies of my slides were distributed and it would be on page 27, but let me refer to how one can actually effect a practical way of using this. I want to emphasize as people have, that no responsible nephrologist of which I am aware, and I certainly would never advocate routine use of intravenous levo-carnitine for hemodialysis. That's a strawman that has been held up for so long as a reason not to cover it for the people who need it for indicated uses. I want to make that very clear, and that was because of the

heterogeneity that the chairman alluded to in a very detailed manner that we have in our units now for several years been following very strict and very detailed algorithms that have to be followed for this to be used.

These algorithms require for example, a cardiomyopathy, and I have to apologize to the chairman. I thought he was asking me how I as a nephrologist used the word and I misunderstood the question, and nephrologists are not cardiologists. A cardiomyopathy as shown in the algorithm refers to sickness of the heart muscle which can take

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many forms, and if one looks at the algorithm for cardiomyopathy, let me just say, if a person has cardiomyopathy, and I apologize that we don't have the slides up, one has to determine if it's the type of cardiomyopathy for which levo-carnitine has been shown to have benefits.

How do you determine type of cardiomyopathy, what subset of heart sickness you have? You do an echocardiogram, that's the practical safe way to do it, it's done in dialysis units now. And you do an echo and if it shows what's called diastolic dysfunction, which is thickening of the heart, which obliterates the heart cavity so the heart can't fill, that has nothing to do, there is no study showing that levo-carnitine improves that. You treat appropriately for diastolic dysfunction things that have been shown to help, beta blockers, CCBs, et cetera.

If you do the echo and you see a certain region of the heart that's not contracting properly, this regional abnormality is not a total heart problem, it suggests that the coronary artery is not delivering blood to that region. That person need to be worked up for coronary

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disease. How do you work people up? The same way everybody else gets worked up, cardiac

catheretization, fix the lesion if you can. Those patients are excluded. We don't want to ever see L-carnitine used as a treatment for critical coronary stenosis; that would be crazy and wrong and bad medicine.

But if you go through that elimination criteria and then you see a person has global hypokinesis, another subset of cardiomyopathy which, this is often what people in slang will call congestive or dilated cardiomyopathy, those patients then get further looked at and we see, have we done everything that's conventional to treat this condition? The patient's volume status control, is their blood pressure on a good control? Have we controlled arrhythmias that they may if we have been able to, and have we applied the other medications that are conventionally applied for this?

And then if we've done that, we reevaluate the patient. We say okay, is it better now? How do you reevaluate? Well, the best way is the echo. And if it's not better, if the patient is still having the same problem, we have

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gone through an illumination and we've tried the therapies, then we ask ourselves several questions. Has the patient been on dialysis long enough to become carnitine deficient, greater than six months? If it's yes, then in our units we measure a level. Now this does properly exclude some people who may be cardiac deficient but not blood deficient, but we have to have standards. And we measure a level, if it's less than 35, then we give a trial of IV levo-carnitine for six to nine months and then we reevaluate, usually by echo along with symptoms. And we reevaluate, we do a reevaluation, and if the echo shows improvement we continue it, if the patient has not improved in terms of symptoms of congestive heart failure on echo, we stop the drug. Thank you very much.

DR. TUNIS: I'm sure there will be more

opportunity for you during the open discussion, several of the panelists will clearly call upon you again in terms of these and other questions.

DR. SCHREIBER: I would be very grateful, thank you.

DR. LINDBERG: I am in agreement with Dr. Schreiber's comments. We have a very strict

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algorithm for starting carnitine. We have actually a check sheet and we have the codes, and we go through the patients on an every three-month basis and reevaluate them in our kinetic session, where we review everything. We at that time review carnitine use.

But basically, what happens to this population is they have kind of become a population that people thought were sick and not worth our time for a long time. I have trouble getting cardiologists or thoracic surgeons to do their CABGs, orthopedics to replace their hips, and they are not the same population they were ten years ago. They are better dialyzed, they have EPO. I have 43 percent of my unit working full time. They are contributing to society, I think you have seen people here, but after a certain period of time, and you have to have corrected everything, they are as, if any of you have listened to the video as one patient said, circling the drain, and this makes a difference. It is a deficiency that as John Newman said when I lectured on this at NPF recently, why isn't everybody on it after they have been on dialysis at least four to five years, which seems to be the

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time when this occurs.

There are a lot of studies, they have been summarized here, and they have very very different types of results, combined results, but this is what happens in this patient population. They aren't easy to study. There are so many confounding variables. I have done a lot of NES

studies, EPO studies, and it's very tough because of confounding variables. The average enrollment in these large FDA studies and companies with lots of money is 2 to 3 percent, because these patients are so difficult to fit inclusion-exclusion criteria.

So these studies are certainly heterogeneous results but when you look at the retrospective review, that's not very heterogeneous, it's numbers. I compared it to when we retrospectively reviewed our calcium phosphorus issues in our patients, and before -- the task before you is to carve out coverage but certainly not to take it away from those who so desperately need it. Thank you.

MR. MEHRLING: I am Ken Mehrling, the chief operating officer from Sigma Tau. I wanted to try to address three things that I think were

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discussed this morning.

One is, the usage prior to the FDA approval has been mentioned several times. I would like to make it very clear that it was not driven by Sigma Tau and I think if you've read some of the outcomes in patient responses, it would not be hard to imagine a physician wanting to try it on more people perhaps than they had done the appropriate qualification. It's a new medicine and it is under review.

That did concern us. We actually funded through the National Kidney Foundation a nutrition study group so that we could end up with a learned group of people to give us advice on how best to have this product utilized. And when our approval came in December of 1999, we actually have incorporated in our promotional materials algorithms, et cetera, that tie back to what the K/DOQI recommendations were. We in no way have intended that this product should be a first line product, nor have we ever intended that it should be routinely used in all dialysis patients. In fact, one of the key points for us is it is not

routine usage but more appropriate usage.
And it was even mentioned with regard

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to the Georgia Blue Cross and Blue Shield policy that there is a subset of patients that it does appear to benefit, and I think that the heterogeneity of study result makes it difficult for us to try to determine who those are, which is why the K/DOQI guidelines have been very helpful and we tried to incorporate them. Thank you.
DR. HOLOHAN: Thank you. I should point out to the panel that Sigma Tau could not have promoted an unlabeled use of an approved drug. That's not legal, so at least from my point of view, I never suspected that.
DR. FORNACINI: My name is John Fornacini (phonetic) and I'm vice president of regulatory science for Sigma Tau Pharmaceuticals. I would like to make a couple of comments regarding this issue. Actually in 12 years that the drug has been marketed, we have a little less than 20 cases of seizures, about 55 percent oral, 45 percent in IV. We put in a package insert the seizure before to get an approval in a (unintelligible) because in a (unintelligible) patient, we only have two or three cases of seizure.
In about two cases -- one case was a

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(unintelligible) seizure. In another case the follow-up showed it was a calcification of the temporal frontal lobe that the investigator classified as a possible cause of seizure. So we can clearly state that more than 95 percent of the cases of seizure were in patients not in dialysis, or patients with abnormal metabolism.
And I want to make another comment about trimethylamine. Some people explained that also trimethylamine can be removed by the dialysis process. That is true, but the efficiency of the removal of the trimethylamines is less efficient

than L-carnitine, because L-carnitine is a (unintelligible) ammonium, so the association is pH independent, is always in a (unintelligible) form, so it is very water soluble. Instead, trimethylamine is vis-avis the association, pH dependent, physiologic pH of 7.4. there is a certain percentage that is disassociated and when it is disassociated becomes very volatile and can be absorbed very easily in very lipophilic tissue. There are studies by Simenov (phonetic) in 1978, that show accumulation of trimethylamine and methylamine in the nervous system, central nervous system, and I remember that trimethylamine anuria

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is a particularly rare disorder due to an impairment of the flavine monooxygenase enzyme that transforms trimethylamine into methylamine oxide, and was associating in many cases -- in some cases, sorry, with seizure. So trimethylamine anuria, an accumulation of trimethylamine in plasma has been associated with seizure. Thank you.

DR. TUNIS: Before we jump into the open discussion, I just wanted to make a couple of comment related to the charge of the panel and some of the things that the panel should be considering or shouldn't be considering.

First of all, since the issue of cost was raised a couple times, I want to make it clear that the factor of cost itself is not an issue for this panel and it's not an issue related to coverage policy development of the Medicare program. Where cost has been mentioned today is that cost is sometimes a factor in whether or not an issue raises to the level of visibility that it ends up being considered for a national coverage determination by either the carriers or by other requestors, but the issue of the economic implications to the Medicare program are not a

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factor that is to be judged in terms of questions

about is this worth doing.

The issue of is this worth doing is to be totally focused on the adequacy of the evidence that you have heard today and that evidence is to include the scientific studies that have been reviewed, the professional guidelines, the expert testimony, and the testimony of the beneficiaries and patients that have spoken today.

So I just wanted to be clear on that, and that the charge of course for this committee is to make a recommendation to HCFA that we will consider in developing the coverage policy for levo-carnitine and your recommendation should be essentially about related to the questions that have been asked here, the adequacy of evidence and we will go through those in the discussion. So we need your recommendation on the adequacy of the evidence in answering the questions about the effectiveness of this product and any other factors that you believe should be considered in making the coverage policy.

So with that as context, I want to give it back to Dr. Holohan to mediate the discussion.

DR. HOLOHAN: Before we actually begin

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the discussion, I'm going to ask Dr. Bonino to come back up, because I think some of the information she provided addresses some issues that have come up repeatedly, including following her presentation. Dr. Schreiber, whom I believe said no responsible nephrologist would prescribe this without going through perhaps not something as ornate as the algorithm he provided us, but that this is something that is at least intuitively done on a regular basis.

And I thought that that seemed to differ from Dr. Bonino's comments about the observation of routine practice in dialysis patients in Pennsylvania, the heterogeneity and regional variability and how that changed with the promulgation of guidelines which as I understand it, and maybe with a little more time you can

elaborate on how these were developed by clinicians in Pennsylvania, not by payers, how these guidelines dramatically altered the pattern of use, and whether in fact these guidelines are similar or dissimilar to those in Dr. Schreiber's algorithm, and whether you believe that the use of these guidelines would provide some criteria for selecting the putative subset of patients who

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would benefit.

That's a long-winded question.

DR. BONINO: I'll try to remember most of it. We did find, and again, it was three years ago in 1998, that the patter of use was very disparate. There were units where it was used in pretty much every patient, and I didn't review every single one of the claims for the 717 patients. Sampling of that does show that there was not what we would love to see, the kind of documentation that Dr. Schreiber is recommending, explaining why it was chosen for these patients. In most cases it was given, and absolutely no documentation about why, outcomes, effect and so forth occurred. There were units where it was never used.

The data that I gave was that of the 174 hospitals in Pennsylvania, and I apologize that I don't have the number of those that have dialysis units. Thinking about the nature of the hospitals we would have now, it's not every single one that has a dialysis unit, but certainly more than ten, and only ten of those hospitals ever used levo-carnitine in that year and billed Medicare for it on behalf of the ESRD patients.

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We had at that time 99 free standing dialysis units and 54 percent, 52 units, ever used the drug. The other 46 percent never used it. So clear discrepancies and differences in use, and we have no reason to believe that the patients were uniformly different between those dialysis units

based on the rest of the claim information.
DR. HOLOHAN: This is probably asking a little bit too much, but do you have data as to whether the mortality rates on dialysis were different?
DR. BONINO: I didn't look to that data, no.
DR. HOLOHAN: Okay.
DR. BONINO: Of the providers, of the 62 providers who at that time used levo-carnitine, 31 of those providers used it in fewer than ten patients, so one would guess that those folks were beginning to use criteria; we didn't see it in the claims.
How do we do medical policy on a local level? Very briefly, it's as I described. Issues are identified through a number of areas, one of which is by high cost, high volume, that's not the only way we identify policies or issues that may

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require guidance.
DR. HOLOHAN: No, but I asked about the guidelines.
DR. BONINO: The input, right. What we did was go out to the Pennsylvania nephrology community, and I have to say something because someone else will if I don't, and it's slightly different for the fiscal intermediaries than the carriers. Prior to 1998, Medicare fiscal intermediaries did not have medical directors, nor did they have well established advisory committees.
We still do not have regulation to describe an advisory committee structure for the intermediaries, so we have used a carrier advisory committee and built upon that to allow us to have access to those nephrologists and to that community. We worked with our ESRD network, which is essentially the PRO, the peer review organization for Medicare ESRD beneficiaries; worked with our carrier advisory committee which has a distinct and well spelled our by regulation

compilation of clinical members, and asked them to number one, give us the same kind of evidence, what's your read on this literature and what's

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your clinical opinion, your expert opinion on how it should be used.

To be absolutely open, we had I would say eight to a dozen letters that came in from nephrologists who supported the use of levo-carnitine. They didn't contain any data or scientific evidence; they were more of the single patient testimonials. But our nephrologists who did review the scientific evidence and then gave their expert opinion, it was the one slide I showed, which was oral carnitine may benefit some folks, primary for the hypolipidemia, it may benefit anemia, but at the time it was thought that erythropoietin was a better drug to use.

And there might be patients who like we've heard described today, who have severe skeletal muscle problems or severe cardio problems, who have been through all the rest, for whom it might be used. Because a local medical review policy is not law, we can pay for those patients to receive levo-carnitine that fit those medical exception criteria. I have not had requests even from those eight or 12 physicians that wrote to me earlier for exceptions for their patients.

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We've had a few that -- the utilization went from, in dollars, 4.6 million six to less than 50,000. In claims, or patients rather, it went from 905 down to 55 patients. So we are paying for some.

DR. HOLOHAN: Let me be sure I understand. This panel of clinicians who for all intents and purposes are all in private practice?

DR. BONINO: Or academic, yes.

DR. HOLOHAN: Not employees of a payor or an insurance company.

DR. BONINO: Correct.
DR. HOLOHAN: Came up with a set of clinical guidelines.
DR. BONINO: Actually, they basically said they wouldn't pay for the IV except for a very rare situation where someone had been through everything else and it was sort of --
DR. HOLOHAN: Well, in terms of the been through everything, was it specified, been through what?
DR. BONINO: I'm sorry.
DR. HOLOHAN: You said patients who had been everything else, and I think the example you were using was cardiac dysfunction?

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DR. BONINO: Right, that basically had gone through the regular standard of care treatments and for whom --
DR. HOLOHAN: Did they specify the regular standard of care?
DR. BONINO: No, but again, this is 1998, and we had planned to take this issue back out, knowing what's going on, but knowing that it came here to a national decision, it's not reasonable for us to go forward with a revision of a local until this is done.
DR. TUNIS: I know that Mitch Sugarman has to leave at 3, I believe. So I was just wondering --
DR. HOLOHAN: We'll just go through.
DR. TUNIS: And I wonder if, Mitch, you want to make any comments or ask any questions.
MR. SUGARMAN: Actually, I have a couple questions for two of our speakers, is that okay?
First, Miss Hernandez, since we are being asked to consider, in addition to the clinical scientific evidence, testimonial, and I appreciate your coming to give that. I just had a question of clarification and then a follow-up

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question. Did your restless leg syndrome begin prior to dialysis?

MS. HERNANDEZ: Yes, that started like 40 years ago when I was a young girl.

MR. SUGARMAN: So it may not be associated then with a carnitine deficiency itself, or carnitine may in some way be of some benefit to restless leg syndrome possibly aside from what it does for patients with ESRD and nothing else.

MS. HERNANDEZ: That seems apparent in my case, because restless leg syndrome became progressively worse, but it did also stop the cardiac arrhythmias that I had.

MR. SUGARMAN: I guess the second question I had was, when the IV carnitine was taken away, did you consider or try oral carnitine either the pharmaceutical type or over the counter from the health food store as a supplement and if not, why not, if so, what effect did it have?

MS. HERNANDEZ: No, I didn't. I did think about it. I saw it, actually in GNC, I thought it was very expensive, too expensive, and I was just hoping that we would maybe get it paid for again. And then after testimony here today, I

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don't think I would want to try oral Carnitor, because of the effects it might have because of what it's broken down to and how the kidneys don't get rid of it, and the possible carcinogen effect of one of their components and what it may do in the gut. I have enough problems already; I don't want to open myself up to more trouble.

MR. SUGARMAN: Thank you very much. I have actually a very similar question for you, Ms. Lewis. Actually, first of, the study that was presented, was done I guess by Dr. Woollen, it's difficult for I think everyone on this committee to take that kind of information into account when you haven't had a chance to look at it in a peer reviewed published form. Has it been submitted for peer review?

DR. LEWIS: That is her plan. This was her -- this was not meant to be sort of, this is a peer review publication. It was just a clinician's account of the impact the policy development has had on their practice, and I think that she plans on doing that, that that's a plan, but this was really to just give an account of, you know, we had patients on therapy for a length of time, they were doing well, we lost coverage

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and we tried to maintain, which they have. I know Dr. Woollen and Dr. Bazemore have talked to me quite in detail about trying to maintain and cover the costs for some of those patients that are currently on. They are a stand-alone dialysis unit and that's what the ESRD program was actually set up for, to help those patients.

MR. SUGARMAN: It is on the surface the kind of study that, albeit it's kind of small, but this is the kind of study that one would like to see.

DR. LEWIS: Exactly.

MR. SUGARMAN: The only other question was, are you aware of whether of those patients who were on carnitine, were then removed or carnitine was made not available to them, did any of them go to oral carnitine?

DR. LEWIS: Yes, there were probably about four of those patients that were on oral for a short period of time, and because of the problems tolerating it, they are no longer on oral, and there was only four of those patients because of costs and other reasons. Dr. Woollen and Bazemore didn't prescribe it for those patients but the patients went out and stated I

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want to have something, an alternative, but there were problems with it too.

MR. SUGARMAN: Thank you. I realize it's anecdotal, but I was curious about that since we're considering anecdotal and testimonial

evidence, I wanted to be clear.
DR. LEWIS: Yeah. If I can make one comment, because we've been told that with this data before, I know Dr. Woollen was very intimately involved with the Blue Cross and Blue Shield of Georgia policy, and this is part of the data that she presented and that was the comment to her, that it's anecdotal, but it is a retrospective analysis. I mean, it's far beyond anecdotal evidence. I mean, it's really one of the only studies that we have that looked at what were the health outcomes when you took those patients off of therapy.
MR. SUGARMAN: I think subjecting it to peer review would be a very worthwhile endeavor.
DR. LEWIS: Exactly. It remains debatable until it's peer reviewed, yeah.
MR. SUGARMAN: Thank you.
DR. TUNIS: I'm just curious, Dr. Paganini, you've been thoughtfully taking all

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this in, and you are our resident clinical expert for the panel. I wonder if you had any thoughts or questions or wanted to weigh in at this point.
DR. PAGANINI: I have been sort of impressed and unimpressed straight through. I came sort of with a fairly open mind. In the clinic where I practice, there are some folks who use it and some folks who don't, and it seems to be used mostly in subgroups of patients that are on dialysis that you've tried everything else and why not try this.
In reviewing the literature for this meeting, I was relatively unimpressed with the outcomes that was purported. However, there is some data that seems to sort of made me more interested. And I would like to ask Jill Lindberg, if I could, a couple of questions, and also like to ask Dr. Kadree a couple questions, if that's okay.
DR. LINDBERG: I don't have my slides with me.

DR. PAGANINI: These are generic questions. During the same period of time that you looked in this retrospective period of folks, you had both those that had greater than two

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months, which was closer to nine months, and then those that had less than three months, which was about two months.

DR. LINDBERG: Thirteen months versus 1.3 months.

(Telephone ringing.)

DR. PAGANINI: You're technologically overloaded, you know that.

DR. LINDBERG: It's a baby sitter, sorry.

DR. PAGANINI: During that period of time --

DR. LINDBERG: My other life.

DR. PAGANINI: The soccer coach or the baby sitter?

DR. LINDBERG: Well, she's trying to get my son to the airport to go to the regional tournament. I was supposed to do that, so that's basically it.

DR. PAGANINI: During that period of time of review, retrospective review, was there a change in KT over V, or dialysis dose delivered?

DR. LINDBERG: Improved URR, and it was in one of the slides and it's in your packet. It was significantly improved URR, and why that may

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be, a higher URR, I can only explain that they may have been eating better because their albumins went up, and higher BUNs and maybe they had dialysis increased. I don't have that individual data.

DR. HELZLSOUER: What is URR?

DR. LINDBERG: Oh, urea reduction rate is a standard we use; 65 percent is accepted by our networks as adequacy of dialysis. We know that adequacy correlates with decreased morbidity

and mortality. I'm sorry, I should have said that.

DR. PAGANINI: The question is actually focused basically for the panelists. There are during that same period of time, there was a concerted effort across the country to try to increase the dose of dialysis, and that increase in dose of dialysis as measured by whatever measure you want to use, URR, a bunch of things, are associated with an improvement in outcome.

And so one of the confounders in this retrospective review is also a concerted effort in improving dialysis. And as such, were both groups improved to the same extent or not?

DR. LINDBERG: No.

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DR. PAGANINI: So therefore, could you define a subgroup in that retrospective analysis that might benefit more by way of patient characteristics from this as opposed to the generic total population?

DR. LINDBERG: Yes.

DR. PAGANINI: And if so, can you withdraw those folks that didn't last the nine months, in other words, they died beforehand, were they withdrawn for a specific reason from carnitine after two months, or did they just die at two months, and so they never really got care?

DR. LINDBERG: 71 I think died -- I'm trying to do it from memory. 71 died at two months, they were not withdrawn. I don't know about the deaths.

DR. PAGANINI: So in effect what you're doing is you're having those that lasted for nine months be self, sort of sequestered, those are longevity people, so you really can't compare the two.

DR. LINDBERG: No, not really, because their hospitalization rate before, when you look at the patient characteristics, and their deaths overall were higher than the control group, they

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were actually sicker, the 13-month group.

DR. PAGANINI: Thank you, Jill.

DR. HOLOHAN: Could I interject and ask the same question, Dr. Lindberg, that Dr. Sugarman asked the previous witness; has this been submitted for publication?

DR. LINDBERG: Yes, AJKD.

DR. PAGANINI: American Journal of Kidney Disease.

DR. HOLOHAN: Submitted but not yet published or accepted.

DR. LINDBERG: Correct.

DR. PAGANINI: Can I ask Dr. Kadree, I was extremely pleased with the way that you handled this question in Georgia, you originally said no and then you said let's take a look at it, and then you had your panel get together as I understand it. The panel then defined a subgroup of folks and then you set up hoops through which people had to move in order to get this paid for. Is that sort of a --

DR. KADREE: Well, I wouldn't call it hoops, I would just say that we required certain documentation to be present on the chart to insure that the drug was being appropriately used.

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DR. PAGANINI: So it would be sort of like an algorithmic approach.

DR. KADREE: Absolutely.

DR. PAGANINI: That you established as policy in order to have this.

DR. KADREE: Right, and I would say that all the documentation requirements are things that have been substantiated in the literature in terms of measurement of those particular quantities for which carnitine is being used for.

DR. PAGANINI: And not to belabor the point of finances, but your group will also allow the payment for these requirements prior to giving carnitine, in other words, if someone needed an echo, you would pay for the echo.

DR. KADREE: Well, all procedures that are medically justifiable are usually covered.
DR. PAGANINI: And if it were to prepare the way for a carnitine --
DR. KADREE: That would be appropriate, because it would be unrealistic and unreasonable to expect them to provide certain documentation and yet at the same time say that it's not going to be covered.
DR. PAGANINI: Thank you. And one

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other question to Joel Kopple, if I could, and then I will stop.
Joel, on one of your slides here, you mentioned that the indications, especially from K/DOQI, that the indications should be fairly restrictive and should only be given to those patients that have a certain list of indications, and then you went ahead and listed indications, malaise, aesthesia, muscle weakness, et cetera, it goes down the entire list through poor sense of well being. Aren't you describing the entire ESRD population with this list, or do you think this can be defined specifically and if so, what percent of population do you believe that this would be addressed to?
DR. KOPPLE: First, Emil, I don't believe that I'm defining the entire ESRD population. It also has to be emphasized that these individuals first must be evaluated as to potential causes and their response to standard therapy has to be evaluated. Not said and not stated by any of these review groups but what I personally would add, and I think it's perhaps misunderstood, is that the person has to have a condition, has to have a clinical condition where

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it might be anticipated that they would have some ability to respond.
What I mean by this for example is if a person for example has disseminated carcinomatosis

for example, if a person has anemia which is resistant to erythropoietin but is also associated with chronic gastrointestinal blood loss, for example from multiple AV malformations, one would not use carnitine.

On the other hand, it's also my perception that you know, those of you who are physicians, probably I don't need to say this, but because you are I think appropriately so, come from heterogeneous backgrounds, let me just say this, that the chronic dialysis patient is a chronically individual. In fact, if you look at the two people who are testifying who in fact are consumers, you can see this just from the way they walk. When we just remember that the death rate of these people nationally is around 22 percent, and often when a doctor is confronted with a dialysis patient on rounds, a person has a bunch of complaints and you don't know what the cause of them are, even after you've gone through a systematic evaluation.

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Emil, am I overstating this? Do you think I'm overstating the condition in chronic dialysis?

DR. PAGANINI: No. I think what I'm trying to do, I honestly, Joel, I think that carnitine may in fact have some significant improvement effects in some patients, and I'm trying to get a handle on who those patients are. And by what you listed here, you know, and I don't think it is supposed to be a debate, but what you listed here, I can sort of list just about all the patients that I have ever come in contact with on dialysis into one of these systems. And yet, the literature doesn't seem to support that, so I'm just trying to get to a handle on who that subgroup might be that would truly benefit and whether or not there is information out there.

There are people who believe in this drug, there are patients who believe in this drug, but when you have to believe in something rather

than actually prove something, it tends to be sort of weak. It's not an EPO, certainly this is not an EPO. EPO was clearly effective in changing hemoglobin hematocrit, clearly effective in changing lives, because that was a major

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improvement. This is not an EPO but it does have a place somewhere, I'm just not sure where, and I'm not sure what subgroup would really benefit from it.

And I'm afraid that if we -- and again, this is just a personal view from -- you know, you guys asked me to come here, and I just think that I don't like to see, I wouldn't like to see this not supported because there are some people who would really, are definitely supportive, and you have heard testimony. On the other side of the coin, I don't think we really know who those people are and until we go through a Georgia type approach where you have very restricted documentation, who's going to do that, who's going to review that, who's going to put that together? That's very expensive and very time consuming, so it becomes most difficult.

As far as use is concerned, it's an education issue. I think when we saw in Pennsylvania where one unit was using it all the time, it was being reimbursed, everybody gets it, that's fine. If it's not reimbursed or reviewed, then nobody gets it. Some units, a lot of people got it, other units, only significant people got

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it. That's education, that's an education of the physician as a provider, and I think that's something that we probably have to address, and I don't think that's there yet.

DR. KOPPLE: May I just respond, because I think in retrospect that slide may have been a little misleading, the one to which you are alluding. I can see how one, it may have be more ambiguous, somewhat ambiguous. I point out, to me

one of the key operative words there is the word potential, and I wanted to emphasize, I was trying to list what most of the publications that I have carefully reviewed, literature have listed as possible indicators. I am not arguing -- for example, I think that the data is particularly weak with regard, I personally believe, with regard to triglycerides; hypertriglyceridemia nonetheless, because that was discussed in the DOQI in the guideline appendix, I listed that as well.

It's my perception that although it would be challenging, I think there are ways in which one could in fact control its usage appropriately and in addition to algorithms, I would point out you could also put a time line on

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it, after which one for example has to demonstrate evidence that it has worked, or however you wish to do it. It's my judgment, in summary, that I do think as difficult as it is, there are ways in which one could control its use. Thank you.

DR. HOLOHAN: Okay. In the interest of time, since the issue with the VA has been raised at least twice, aside from my claiming Dr. Chakel as one of ours, before Mitch Sugarman has to leave, I wanted to make a comment about my investigation of the use in the Veterans Health Administration of parenteral carnitine. First, the issue of benefits in the VA is rarely if ever driven by dollars. If you talk to the American Legion or the Paralyzed Veterans of America or other groups, they will make that argument to Congress, but medical care is not determined on the basis of costs.

VA has for many years had a total drug benefit, oral, parenteral, it makes no difference, all drugs are provided. Prosthetics are provided. You can have your home or vehicle modified free if you are disabled; the VA buys you run-flat tires so you don't have to change your tire by the side of the road, et cetera. The point I'm making is

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that money is not a major consideration in the provision of care in the VA.

Parenteral levo-carnitine is not on VA's national formulary. The national formulary in the VA is determined by a medical advisory panel, which includes all clinicians and some pharmacists in the Veterans Administration. Requests for additions to the national formulary come from the ground up. They occasionally come from industry, but that's uncommon.

So items that are put on the national formulary are put on the national formulary because doctors in the VA and some pharmacists in the VA believe they are needed. Despite criticism, our national formulary process and its existence has been as you might expect, reviewed by every imaginable alphabet soup government agency. We have had a review by the Institute of Medicine that took two years. We have had an inspection by the Office of the Inspector General of the VA, and we have had a review of the formulary process by the General Accounting Office. All of those have endorsed the national formulary process as clinically driven, evidence driven and reasonable.

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I spoke to our field advisory group in nephrology in the VA two days ago, and it is the general belief of the nephrology field advisory group that there are few if any proven indications for the use of parenteral carnitine. If Medicare wishes, I can give you the names of the people who provided me that opinion.

I should hasten to add, one of the physicians who made that statement has himself been a hemodialysis patient for 17 years, Dr. David Cohen, who is chief of nephrology at the West Palm Beach VA. So in general, there is not the belief among nephrologists in the Veterans Health Administration that this should be

routinely or even rarely used in patients on carnitine ore dialysis, and it does not appear on our national formulary.

A small number of patient have been given it, you can request an exemption from the national formulary for local use, and that is granted 96 percent of the time, according to the Institute of Medicine study.

MR. JOHNSON: That was my question, Tom, does it require prior authorization?

DR. HOLOHAN: Yes. Any clinician in

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the VA can request an addition to the formulary. The local formularies of networks, of the 22 networks, can be more extensive than the national formulary, but they have to include every item on the national formulary. They can be more expansive but not more restrictive.

MR. JOHNSON: As a follow-up, I wonder if Mitch, I know that Kaiser has a very good formulary process; is carnitine available at Kaiser?

MR. SUGARMAN: Sometimes I call Kaiser kind of a mini-VA or mini-HCFA, but I'm not sure it's really like that. The fact is that Kaiser, because we have at the moment eight different regions, we have eight different formularies. For all intents and purposes, the only ones you really want to think about very much are northern California and southern California. Levo-carnitine is on the formulary in northern California, it is not on the formulary in southern California, so where does that leave us. It is about as consistent as the VA or --

DR. HOLOHAN: The VA is consistent.

MR. SUGARMAN: I'm sorry. About as consistent as Medicare. I did check with a number

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of our nephrologists and a number of our ESRD folks before coming here and in both northern and southern California, it is rarely used. They put

it on the formulary in northern California because it was FDA proved and there are other indications for it. In southern California where it's not on the formulary, like with the VA, you can make an exception policy for a patient. So, it is somewhat discretionary.

I will say that because our patients go into our hospitals, a reduction in hospital stay would be a significant cost savings to us, so I think if our experts in this area really felt that there was a significant benefit to putting patients on this, we would see it used a lot more. You know, it's not as though they are just looking at the cost of levo-carnitine. When a patient of ours goes into one of our hospitals, there is a significant cost to us there as well.

DR. JORDAN: Just a question, and maybe a stupid questions; I just wondered between the VA and Kaiser, is there any difference in the population of people that may need levo-carnitine, meaning, do you have as many ESRD patients as the Medicare population does, and is that a reason why

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your policies and/or the potential that you're he seeing less of it used is affecting your experience, or does Medicare know such questions?

DR. HOLOHAN: We have a far smaller number of ESRD patients than does Medicare, and there are many reasons. Despite the fact that VA had dialysis essentially universally available long before 1976. VA also did the first kidney transplant in the world. Just another shameless advertisement.

But what has happened with the passage of the requirement in 1976, right? No, no, no, the ESRD --

DR. PAGANINI: '73.

DR. HOLOHAN: '73, okay. Patients have a lot more choices and if it means traveling two or three hours to a VA hospital from Salem, Massachusetts to Jamaica Plains, when you can go to, and I don't mean this facetiously, but the

Acme Dialysis Center which is across the street, and you have Medicare benefits for that, the patient will choose what they wish, as they do with coronary bypass graft and anything else where they have dual eligibility, so our patients are much smaller in number.

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MR. SUGARMAN: I'm actually not certain what our number of ESRD patients is, but there is another factor I guess that's worth considering, and that's that at Kaiser, greater than 90 percent of our Medicare patients are Medicare plus choice and they are at risk, it's an at risk population, which means that they have a drug benefit. So whether this group decides levo-carnitine IV or not, if a Permanente physician decides to write for levo-carnitine, it's a covered benefit. In other words, for Medicare an oral dose becomes a nonissue, the cost is zero; for Kaiser or Medicare members, that's not the case, so it's somewhat irrelevant to Kaiser I think what decision this group comes out with.

DR. TUNIS: Before going too much further, it would be useful for me at least to hear some discussion of what is the clinical entity of carnitine deficiency? Eventually we're going to have to vote on something to do with it, that has the adequacy of evidence that there is a treatment for carnitine deficiency, and I'm not yet clear and I don't if maybe the rest of the panel is, on what the syndrome is. So I'm wondering if one of, maybe Dr. Kopple or

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Dr. Chertow or someone could venture to describe the entity that is carnitine deficiency. My guess at it is that it's below a certain serum level of carnitine with some of a long constellation of potential symptoms that may or may not be associated with that, but I'm, I would rather hear the official version.

DR. CHERTOW: Perhaps I will state what

we don't know and then allow Dr. Kopple to state sort of what we do. What we lack beyond some of the biochemical parameters are as we phrased in the DOQI guidelines, an outcomes approach. We don't have a population based survey where we could link either free, total, or other ratio carnitine levels to a variety of clinical parameters, be they ejection fraction, quality of life, any number of clinical factors. I think that kind of study is sorely needed.

DR. TUNIS: Can I have more on that, because this actually goes directly to the issue of, I don't understand how the FDA could use serum level of carnitine as a surrogate marker when you're telling us that there is no relationship between carnitine level and any clinical outcome measure. My understanding of surrogate markers is

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hypertension is a surrogate marker for risk for heart disease or stroke, because there are hundreds of studies that link different levels of blood pressure to differential risks for certain clinical outcomes. And I was curious as you were talking about the surrogate measure, and I don't know if Alexander Fleming is still here, and whether that's the original Alexander Fleming, but whether someone could speak to how the FDA determined that this would be a surrogate marker for carnitine deficiency.

DR. FLEMING: I want to emphasize that I was not directly involved in any of the approvals for the indications related to carnitine, but I think it's safe to say that given the size of the patient populations and the plausibility of the benefit, given what was known about the specific metabolic deficiency states, that it was concluded that this did represent a surrogate that is meaningful and could be depended upon for basing the NDA approval. Now, the fact that the FDA did not require an additional study or studies to be performed as a follow-up to the approval that was granted for ESRD related

carnitine deficiency I think indicates the Agency,

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going back to your interest in kind of a grading scale, felt that this was a situation where the evidence was relatively strong as things go, and taking into account again the difficulty of doing studies that would be any more definitive.

DR. HOLOHAN: Can I ask you to clarify something? You said the evidence was relatively strong. Do you mean the evidence from the point of view of the FDA was relatively strong that parenteral levo-carnitine would increase blood levels of carnitine?

DR. FLEMING: Well, certainly that's established, there is no issue there, but I think what I'm talking about is substantial evidence of clinical outcomes taken, you know, kind of meta-analysis that suggests that there are benefits likely for patients. Again, with the surrogate outcome, almost by definition, you can't have at the time of approval, clinical confirmation of the benefit, so it comes back to what is biologically plausible, and that's really the key here, is excellent plausibility for the surrogate given the understanding of the pathophysiologic state, the expectation that patients who have severe carnitine deficiency

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because of dialysis and have symptoms that are reasonably ascribable to carnitine deficiency, when their deficiency state is repleted that they would benefit.

DR. TUNIS: Okay.

DR. HOLOHAN: Well, I'm more confused now Sean than I was before, because the letter from the FDA says, the date clearly support the efficacy of intravenous levo-carnitine in maintaining or increasing carnitine serum levels in ESRD patients on dialysis. They do not support improvements in clinical status or exercise tolerance, et cetera, et cetera. So it sounds to

me as though the FDA said the data support IV levo-carnitine to maintain or increase carnitine serum levels in ESRD patients on dialysis, and didn't reach to clinical status, exercise tolerance, B-1 creatinine, et cetera.

DR. FLEMING: Yeah, I think that's an important point that deserves some detailed discussion. A distinction was being made there by looking at the primary outcomes that were explored or examined in the pivotal studies. What ultimately was concluded and is documented in the record, is that the studies that were performed

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were underpowered in retrospect, to provide definitive results with respect to the various outcomes that would be considered clinical benefits.

Now you're quite right, that by pointing out that those particular parameters had not been proved, the Agency felt compelled to include that information in the label, and they did that for the reason that I tried to explain, that is, to give physicians some perspective on the basis of approval. It was not to say that substantial evidence was not available, and I emphasize that, substantial evidence in toto was available, most of it, 90 percent was yes, the effect on the surrogate outcome, the repletion of carnitine levels. But I do think, and this is my perspective, my judgment from reading the record and reading between the lines, that the clinical reviewers felt that there was great plausibility of clinical benefit based on what was actually shown in what we would call the secondary body of data.

COMMISSIONER GRANT: Can I ask a follow-up to your question? This letter also says that clinical manifestations do not ensue until

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the level falls to less than 20 percent of "normal". Now, what is normal, and is that, was

the finding that in fact use of intravenous reestablishes a "normal", and if you crosswalk to the document presented by Sigma Tau, they actually give amounts that are "normal", and is that relevant to what we're talking about, if we're trying to figure out what a deficiency is? I mean, if that's all that is being established here, that is, a nondeficient situation which goes to normal?

DR. FLAMM: Well, you know, that's another perceptive question, because in my former business, we always made a distinction between a therapeutic approach that involved a kind of, well basically a pharmacologic approach, and one which was simply repleting a deficient hormone state. So in the case of some hormonal deficiency states, we would accept that just by virtue of showing a repletion, a normalization of plasma levels of that hormone, that you could accept that as sufficient for approving an indication for that hormonal replacement therapy.

We could have asked that a number of long-term outcome studies show that indeed by

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replacing the hormone in what has to be an artificial manner, that indeed, there is clinical benefit ultimately. But the Agency was always more reasonable when it came to starting with a deficiency state, using a therapy which in effect was an endogenous compound that could correct that deficiency state.

COMMISSIONER GRANT: Is that what's going on here?

DR. FLEMING: Well, I think it does tie in with the idea that the surrogate was plausible, biologically plausible, an observation of normalizing of depressed carnitine levels was observed and that in itself reaches a certain threshold of evidence, and ultimately accounted for a good part of the weight of why the Agency approved the therapy.

DR. TUNIS: Well, maybe Dr. Kopple, you

could just clarify for me which of these two alternatives is right, or if they're both wrong.

DR. HOLOHAN: Can I interject for a minute? I thought Commissioner Grant's question was pretty straightforward and that is, is 20 percent a cutoff, 20 percent of normal a cutoff for when one should see clinical manifestations of

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carnitine deficiency, as the FDA alleges? And if that's not a reasonable definition of carnitine deficiency, what is and what's wrong with the FDA's guidance? Have I misstated what you were asking?

COMMISSIONER GRANT: No, because I was trying to follow up on your question of what are we looking at here.

DR. TUNIS: That's what I was -- maybe Dr. Kopple, but anyone else can fire in, is it that carnitine deficiency is, you have to be 20 percent or below normal and have some list of symptoms associated with that, or is every patient with ESRD on dialysis with an unexplained symptom potentially carnitine deficient, or a third option which I don't know what it is?

DR. KOPPLE: One of the difficulties in coming to conclusion on this problem, and one of the reasons that I think that the panel was convened in the first place, is because unfortunately there doesn't seem to be a very obvious syndrome in which you can identify who is going to respond and who is not. Unfortunately, if in fact carnitine does have a benefit, it just, it is not -- the individual who may benefit from

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carnitine cannot be identified by a physician walking into the room, examining the patient, or running a simple blood test.

And my suspicion is that again, if it's beneficial, then this is one of the reasons it's been so hard to identify this subset who benefits. As a result of this conundrum, different -- there

is probably no single way in which everybody -- there is no single way, I will tell you, in which every nephrologist would treat a dialysis patient with regard to starting or not starting carnitine therapy. It doesn't exist, and if you have looked for this in literature you will see that you haven't been able to find it.

Now, so I can suggest an approach, but I would emphasize two things. First of all, it would just be my idea, and second, I'm not sure that I'm right. In fact, I have a favorite statement, I'm always impressed with how often my ideas turn out to be wrong. But I think some combination of a low plasma carnitine level, if for no other reason than the FDA mandates that as an indication for using carnitine therapy, in association with one of several classes of symptoms or signs for which the patient has not

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responded to any conventional therapy.

And in addition, for which there is reasonably that the patient does not have a condition which would prevent the potential response to carnitine, such as in the case of erythropoietin resistant anemia, GI bleeding which cannot be stopped. There are many such conditions in our patients.

And I mentioned the word clusters. In my opinion, these clusters would include the following: One related to skeletal muscles, there's a whole series of different manifestations that are described in the guideline. The second is myocardial, certain types of cardiomyopathy. The third would be intradialytic, occurring during dialysis, cramps or hypotension, again, that can't be explained by other factors such as aggressive removal of fluid in order to bring the patient's water balance down to a healthy level.

Another would be, erythropoietin resistant anemia, whether hypertriglyceridemia, that's elevated certain triglycerides, should be on the list or not I think is debatable. But I

think that's about the best I can do, and what many people have done is that they will give a

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trial therapy and use the response to the clinical trial as itself, a diagnostic test.

DR. HELZLSOUER: Before you go, I have a question, because it was brought up before that, I heard one comment saying that after four to five years on dialysis, everyone is carnitine deficient. Is that true? I'm trying to get an idea of what percent of the population is appropriate for it. You talked a lot about appropriateness, so do you uniformly, does everybody become carnitine deficient on dialysis? If not, what percent do?

DR. KOPPLE: If you define by carnitine deficiency a reduction in total body carnitine pools --

DR. HELZLSOUER: Well, we have this one definition that we're talking about here of less than 20 percent.

DR. KOPPLE: It's nowhere near everybody. At that level, Dr. Fornacini probably give you a number but I would give you an estimate. It's probably around at that level, maybe 10 percent. John, what would you say?

DR. FORNACINI: I would --

DR. TUNIS: I do have to -- we are sort

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of in the panel deliberations so the only folks who can speak, unfortunately, are folks to whom one of the panelists has directed a question.

DR. KOPPLE: There are better people to answer your question than me. I would guess it's around 10 percent are at that number. As I said, I would not personally use that number alone as a basis for treatment, I also would like to see somebody with one of these disorders that did not have another cause or did not respond to more conventional therapy.

DR. TUNIS: Do you want to ask someone

else that question as well?
DR. HELZLSOUER: No, that's all right.
DR. HOLOHAN: Commissioner Grant, did you want to ask your question or anybody?
COMMISSIONER GRANT: No. I'm taking this in.
DR. TUNIS: I did have a question for Dr. Chertow, who keeps trying to get out of these, but I'm going to keep pulling him back in. It seems from looking at the most of the dates of the literature that has been reviewed that most of the information we have looked at today was available to your subgroup of N/DOQI, so am I understanding,

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and you can clarify this, that that was a fairly highly expert group both clinically and methodologically in the area of nutrition and nephrology, and so with essentially the same body of evidence, maybe missing a few very recent studies, their sort of conclusion was as you gave it, which -- and it sounded to me like one part of it that I remember, but maybe you could restate it now since it was a long time ago, one part was that it seemed that the most promising clinical use might be for EPO resistant anemia, but what was the more general conclusion of that particular group looking at this data?
DR. CHERTOW: Well, for a moment of background and to bring in what other people have said since I came this morning, I agree with Dr. Lindberg that conducting clinical trials in patients on dialysis is extremely difficult, and I did mention briefly in my presentation that many of the proposed indications for L-carnitine are difficult to measure ones, things like asthenia and muscle strength.
On the other hand, we have more than 200,000 dialysis patients in the United States, and cross-sectional studies linking relevant

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clinical outcomes if you will, or clinical

parameters to carnitine levels is not a difficult study to conduct. And in addition to the paucity of randomized clinical trial evidence in support of the routine use of carnitine for a variety of these indications, we were also struck by the absence of the outcomes data that we have come to enjoy in cardiovascular disease, oncologic disease, and other diseases which the panel is familiar, perhaps more familiar.

You're a professor of epidemiology at Johns Hopkins, obviously the serum levels are at least a second order surrogate outcome, and as an epidemiologist, I wanted more first order surrogate outcomes in order for us to have more enthusiastically endorsed the use of carnitine. While plausible, and clearly plausible and clearly of concern to us, which as other people including Dr. Fleming have mentioned, the absence of more direct links was a concern.

DR. TUNIS: So was it the sense of that panel though, that some of what's been expressed here, that there seems to be some clinically appropriate use of L-carnitine in some subset of patients but it's hard to define who they are,

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what the indications would be, but it seems to have some use, and the most promising of those some potential uses is EPO resistant anemia. Is that a fair statement?

DR. CHERTOW: Well, for instance, anemia is a broad condition that requires therapy and is complex in its management in ESRD patients. The clinical finding of being erythropoietin resistant is an observable tangible clinical finding that then we can target, for instance. In the other indications, we didn't have the other links to the more distal outcome like anemia. For instance, in muscle strength, we didn't have a study that said if the muscles are X size or in X type of person, or a muscle biopsy characterized by X would then predict a response.

I think in the erythropoietin resistant

anemia example, we at least could identify a subgroup of patients or subjects who were not receiving adequate or optimal outcomes, and they could be identified as something tangible.

DR. TUNIS: One last point to make about the Rand methodology I don't think a lot of folks are probably familiar with, but it's a modified Delphi technique, which is essentially a

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quantitative method of consensus development using sequential scorings on a scale from one to nine. It's a very well described consensus development technique that takes into account clinical literature, but it's not -- in a sense, it deviates from a standard evidence based approach which only will look at the trials. So had there been strong consensus without any evidence amongst the nephrologists or the experts in your subgroup, that would have been reflected in a strong recommendation in favor of something, or did I characterize that correctly?

DR. CHERTOW: No, no, that's correct. Had the group decided that a score, if I'm not mistaken, of either seven, eight or nine had been not unanimously but nearly unanimously decided upon by the group, that it would have received a more favorable endorsement.

Just let me clarify that while there was a subcommittee within the committee that focused efforts on carnitine, the entire committee voted on the guideline statements which ultimately became one major guideline statement.

DR. PAGANINI: May I just enter, and correct me if I'm wrong, but if that were the

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case, that that statement would in fact be bracketed at the end, and say opinion based or not. In the DOQI guidelines when there were clear evidence, it was evidence based. When they were clearly, when the predominant thought process was opinion, it was identified as such, as opinion

based; is that right?
DR. CHERTOW: Right. If I'm not mistaken, this guideline was designated, while evidence was of course considered, that the guideline statement itself was deemed to be opinion based from the group.
DR. KOPPLE: I think it was both.
DR. TUNIS: Thank you. At some point here, sort of the last phase is to turn these questions, and everybody already has their one-page list of questions, at some point we have to actually turn these into a proposal for language that we will then vote to approve or not. And the language can either be exactly what's here, formed in the manner of a proposal, or you can choose as a committee to amend this language and then vote on it. So, if you walk, Tom, you can sort of walk folks through these questions and call for a motion basically of either the

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statement in the form of a question, just like Jeopardy, or a modification.
DR. HOLOHAN: Okay. Having read these questions, they are probably, don't demonstrate the clarity to me now that they necessarily did this morning, and let me explain why.
We begin by talking about evidence that the administration of intravenous L-C is effective as a therapy. I think the issue raised earlier by probably I guess yourself and Commissioner Grant may preceded this, and that is, what is carnitine deficiency? And I am wondering, and I will ask the panel for their opinions on this, should the first question be, can we identify a group of patients, a characteristic of a group of patients who have carnitine deficiency and then would be reasonable candidate for administration of supplemental carnitine by whatever route?
DR. HELZLSOUER: I'm not sure we're capable to define carnitine deficiency. The FDA had a definition based on blood levels, and then the question is, we've heard that it is not

adequate. And that was my question earlier on in the day, at the first presentation, what is this entity, and it's clear that it's not well defined,

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even before we get to the evidence.

The evidence that we have before us is very inconsistent, and none of those studies talked about a clear definition of carnitine deficiency, it was based on symptoms.

DR. HOLOHAN: Right, symptoms or --

DR. HELZLSOUER: For end stage renal disease patients.

DR. HOLOHAN: Or some clinical outcomes, maximum exercise capacity, what have you. I guess I'm asking for the consensus of the panel, or a majority at least, as to whether the issue of the definition of what is carnitine deficiency is important, critical, or should be ignored in favor of just looking at the bodies of available evidence that look at clinical measurement of one sort or another. Should we poll?

MR. JOHNSON: I think the latter is where I would come down on it. I don't think the evidence is clear.

DR. HOLOHAN: So you would not be in favor of attempting to address the definition of carnitine deficiency?

MR. JOHNSON: Correct.

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DR. HOLOHAN: Dr. Paganini?

DR. PAGANINI: I don't think I would like to try to define it, but I do believe that the data shows the clustering of improvement in some patients are rather dramatic and in fact may have carried some of those marginal studies because of a larger end, so I think that there is buried there evidence of improvement, sometimes drastic improvement, in some patients. My problem with this is identifying those patients a priori to getting the medication, as opposed to those

that are proved after a blanket deliberate medication.

DR. HOLOHAN: Dr. Helzlsouer?

DR. HELZLSOUER: Well yeah, I think as I just said, that I don't think we're in a position to define carnitine deficiency given the information we have and I agree, where I'm coming down to is I think the literature as a totality is very poor, studies when they are there are poorly designed for the most part, not all, so there may be some who benefit. And I know that it's difficult to do trials, it's difficult to do trials in any patient population, but you owe it to the patient population to do this, and to those

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who I've heard how difficult it is, I'd say you really owe it to your patients to try to sort this out, and the problem we will be faced with is defining in some way who might benefit from this.

And I agree with what you just said, but I'm not sure we have the capability to define, if the experts can't tell me what carnitine deficiency is, we won't be able to sort it out this afternoon.

DR. HOLOHAN: And by default, I presume you are not willing to accept the FDA definition.

DR. HELZLSOUER: Well, I just heard from the experts that that's not in and of itself appropriate, just by a percentage alone, but that certainly would be, a definition of any deficiency, you would have a cutoff value where you should replace.

DR. TUNIS: Faced with a similar problem last week related to the issue of no existing good definition of the syndrome of suspected white coat hypertension when we were looking at ambulatory blood pressure monitoring, they took the approach of making a recommendation about the adequacy of the evidence, but essentially recommending that coverage not begin

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until HCFA working with the professional universe developed a definition for suspected white coat hypertension. And this panel could consider an approach analogous to that, which is to say that we acknowledge that the entity is not well defined, we'll vote on the evidence such as it is, assuming that there will be an operational definition for carnitine deficiency that HCFA will work with the professional associations to develop. That's just the way we dealt with a similar problem in another context.

DR. HOLOHAN: I didn't want to get there that fast, but you have made the point, Dr. Metzger, about the definition of carnitine deficiency.

DR. METZGER: Being a bureaucrat, I'm looking at one of the company's supplemental submissions subsequent to the original approval, and they mention, currently a range of 40 to 60 nanomoles per milliliter in blood is considered normal carnitine range, and if you take 20 percent of that of the lower, or the mean, that would be 10, but that would just be something to hang your hat on as a minimum amount, in addition to other symptoms or signs.

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DR. HOLOHAN: Commissioner Grant.

COMMISSIONER GRANT: Well, I had my logic, before I lose it. And having sat in on the panel -- was this the Executive Committee?

DR. HOLOHAN: Yes.

COMMISSIONER GRANT: So having sat in on the panel at a lower level, I guess I'm going to come out a little different on that. It seems to me in this case that since the FDA approach for approval for an indication doesn't appear directly relevant to what we're hearing clinically, because clinically it sounds like there is a constellation of symptoms that emerge. We do have another body of evidence frankly in the hierarchy which goes back to the K/DOQI approach, that's the guideline approach, which is somewhere in between certainly

the body of literature that we don't have here and the white coat hypertension, where there was some guideline conversation, but I think K/DOQI guidelines here seem closer to allowing one to proceed.

And I have a problem at this point in the deliberations of saying not to proceed because we're also so much out in the environment in providing coverage for this and as a practical

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matter, I am very bothered that we heard for the first time today a couple case reports or however we characterize them that unfortunately haven't gone to peer review, and that's very troubling, if indeed there is enough information and the dilemma is how do you not hold up the process but strongly signal that if there is real data out there, then beneficiaries deserve that, to go to publication or not.

So I would -- you understand what I'm saying?

DR. HOLOHAN: You sound like Dr. Helzlsouer saying that -- are you saying you owe it to the patients to complete --

COMMISSIONER GRANT: I think that we have, we can't hang our hat on FDA in this case, but we do have the K/DOQI approach, albeit needing some more specification, so one could charge that group, which apparently spent a lot of time and energy in thinking about that, to be more precise, but that's a little different from postponing indefinitely, which was the case you talked about, so I think we could substitute the K/DOQI.

DR. TUNIS: Yeah, just, that actually was -- the EC's formulation was to actually say,

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in ambulatory blood pressure to say yes, there are situations in which it should be covered, and you can go ahead and proceed to do that assuming you work out, and that's not postponing it, that we will work out the definition.

COMMISSIONER GRANT: That's what I recall the lower group coming out with, but I thought I heard something different.

DR. TUNIS: It was assumed that it would be done in the time frame of when the coverage decision was due.

DR. HELZLSOUER: So the issue here would be that it would be up to you to define the subgroup of patients, or come up with a means to do that. Is that feasible, would you be comfortable with that?

DR. TUNIS: Well, it's a little bit by default that if the committee can't do it, then --

DR. HELZLSOUER: Somebody has to do it.

DR. HOLOHAN: Well, I don't want to speak for the panel, but I'm getting the feeling that people are kind of trying to arrive at a verdict that a British but not American jury can arrive at, which is not proven. You're not innocent, you're not guilty, we can't make a

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definitive statement that there should be universal coverage or there should be universal noncoverage. Is that it, or am I putting words in people's mouths?

DR. JORDAN: Well, on the definition of what a deficiency really is, one of the things that concerns me is the uneven application of policy that's going on right now in this patient population, and the fairness of that considering where the evidence lies, and what we've heard. I think it's critical that there be a national policy established that goes in one direction or another, and I happen to be leaning toward, because of I think the fact that we're pretty far out there on permitting a large number of patients to use these products and there are at least some that are benefitting from it, that until HCFA can establish some reason to exclude some population, that we're going to have to be more lenient on its use.

So I guess, you know, whether not

proven is an adequate response from the committee, I don't know. It doesn't summarize where I am, I guess.

DR. HOLOHAN: Sorry.

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COMMISSIONER GRANT: I was just saying the literature doesn't prove it, but the weight of the consensus panel by default, we don't have peer reviewed literature that proves it clearly, in my mind. We do have a strong clinical sense that I'm hearing, relying on the sense that this consensus group has, the way it was described as a coalition of a number of organizations, although they clearly didn't go far enough in specifying to be helpful, but it's hard to walk away from even that limited, albeit limited recommendation.

DR. JORDAN: There was a suggestion by Dr. Chertow that maybe we could establish some better evidence with a relatively simple trial. Is it possible that HCFA in its policy could set up some guideline, some hoop that requires the measurement of carnitine levels in people in a more routine manner so that we can begin to develop the body of evidence that might permit the exclusion in certain cases where there is inadequate evidence. They ought to be trying to define that in some way for those patients; we owe it to them I think was the words that Kathy used.

MS. DOOLEY: I also think what I have heard a number of people say is that the data that

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has not been peer reviewed may be helpful on that. I mean, it's just unfortunate that data, when it's not peer reviewed at this point in time is not considered or weighted as much as published data, but yet, you don't want to be making a decision if there is poor data or unpublished data that actually could help you further define that.

DR. TUNIS: Well maybe for the sake of moving further, we could try to stipulate at this point that we'll assume, we will make the

assumption that there is a definable entity of carnitine deficiency that we will not define here today but that will be defined following this meeting through a process that be HCFA will work with either MCAC and/or other appropriate groups. And then maybe what you should look at, you know, someone proposing --

DR. HOLOHAN: Do you want someone on the panel to make a motion to that effect? Because I don't think you can.

DR. TUNIS: Sure, why don't we have it as a separate motion, or some version of it.

DR. JORDAN: I move that HCFA establish a process whereby they define carnitine deficiency, because sufficient evidence exists

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that such a condition exists.

MR. JOHNSON: And that would include the experts in the field, the DOQI group and so forth, that would participate in that process?

DR. JORDAN: Right.

MR. JOHNSON: I would support that motion. I second it.

DR. HOLOHAN: Any discussion?

DR. TUNIS: Kim has to go through some formality about mentioning the voting members that are here and stuff.

DR. HOLOHAN: Oh, okay.

MS. LONG: The voting members present at this time are Kathy Helzlsouer, Robert Johnson, Ronald Jordan, Emil Paganini.

DR. TUNIS: Okay. And I think Kim didn't get the wording for the motion, so could you, Ron, just try to repeat it?

DR. JORDAN: I move that HCFA establish a mechanism to define carnitine deficiency in the ESRD patient population because adequate evidence exists that such a condition exists.

MS. LONG: Correct me if I missed something, please. The motion is for HCFA to establish a mechanism to define carnitine

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deficiency in the ESRD patient population because there is adequate evidence, or adequate evidence exits?

DR. HOLOHAN: That such a condition exists, i.e., carnitine deficiency, truly exists.

MS. LONG: Okay. All those for, please show a hand. All those against. It was unanimous.

(Unanimous in affirmative.)

DR. HOLOHAN: Okay. I'm sorry to bring up the question of the definition, but I thought that logically preceded the other questions posed to the panel. Bear in mind, the panel should bear in mind that these are suggested questions and you can change them as you see fit or disregard them entirely if you also see fit.

The first question is, is there adequate evidence that the administration of intravenous L-carnitine is effective as a therapy to improve clinical conditions or outcomes in patients with end stage renal disease on hemodialysis?

And in considering this question, you are asked to consider the evidence both overall in aggregate as well as be specific clinical

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conditions such as anemia, disorders of lipid metabolism, cardiac dysfunction, disorders of muscle strength, physical functioning or exercise capacity, or inter or intradialytic complications, and patient well being, and the examples given are fatigue, muscle cramps, intradialytic hypotension, or quality of life.

Is there any discussion as to whether this question is appropriate for the panel to address and attempt to answer?

DR. PAGANINI: Mr. Chairman, I think what you're doing is defining a population and I think, wasn't that what we just voted on, was to define a population? The rationale behind that statement is that if you read the statement as you

read it and as it's printed, then we are also supposed to go through each of those subgroups. I suspect that that would be part of the definition of the population that in fact has carnitine deficiency and therefore, our first motion would include the definition of that. Otherwise, you would have to change the original sentence to improve clinical conditions and outcomes in some patients, or in a subgroup of patients with ESRD, as opposed to all ESRD patients.

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DR. HOLOHAN: Okay. So you would simply add the words, in some patients, in 1-A?

DR. JORDAN: Well, he's also saying it may not be necessary based on the first motion to even answer this question, because the process would be --

DR. HELZLSOUER: Well, I think it would be those patients with the defined condition, along with carnitine deficiency.

DR. HOLOHAN: Okay. So, the reason I went on from that to this is we had testimony that carnitine deficiency defined as levels was inappropriate, that there may not be, it may be that the best available evidence and opinion that HCFA can collect will still not adequately define a population.

DR. PAGANINI: I think the charge to HCFA was in fact to define carnitine deficiency not only by a blood level, but by utilizing all means possible to define that patient subgroup. I suspect that patient subgroup may be some combination of blood and symptomatology and so therefore, one or the other or both, but certainly not neither, and so I suspect that by doing that, we would have answered that and if in fact that is

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a subdefined group, then carnitine, the evidence of that defined group may well then be adequate in those studies we've seen and in those studies yet to come to be covered, so I would have no problem

if this original sentence was in carnitine deficient patients in ESRD, or in a subgroup of patients in ESRD, or something along those lines that would define what we asked HCFA to do in our first resolution.

DR. TUNIS: That sounds like the sort of question we do need to ask you to answer, which is in patients so defined, however that is from your first thing, is the evidence adequate, and then how the rest of this is phrased, you know, either in aggregate, taking some universe of symptoms or for these individual symptoms, of which you saw tables of data on, cardiovascular, anemia, et cetera. So those, I think, are the next series of questions, but modified as you modify them.

DR. JORDAN: So you're trying to narrow down the universe of what HCFA needs to look at?

DR. TUNIS: No, we're just trying to say, we'll take care of defining some group, but you still have to vote on the adequacy of evidence

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that treatment of that group --

DR. JORDAN: In these conditions that are listed.

DR. TUNIS: Right.

DR. HOLOHAN: All right. I think Dr. Paganini's point, and correct me if you think I'm putting words in your mouth, is given the fact that we yet don't know which patients in which of the studies that have been reviewed in fact were carnitine deficient, that it's impossible to answer that question pending the definition that HCFA is expected to provide. Have I rephrased what you said?

DR. PAGANINI: That's correct.

DR. HOLOHAN: So what he is saying is that question 1, both A and B, is not answerable. Let me again explain, and correct me if I'm wrong. I think what Dr. Paganini is saying is that we have reviewed painfully a large body of published studies which are in the main of mixed quality.

Some of those patients may have in fact had true carnitine deficiency, some of those patients may not have had true carnitine deficiency, definition to be provided. And until we are able to stratify those patients on the basis of something other

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than a disorder of lipid metabolism or a reduced exercise capacity, we don't know whether the reduced exercise capacity was in fact related or not related to carnitine deficiency, so it's impossible to answer this question unless you can specify the particular group of patients of concern.

DR. HELZLSOUER: But even if we specify that, given the evidence we have now, we still wouldn't be able to answer it, so basically we're saying the evidence is insufficient, I would think.

DR. HOLOHAN: Well, I was trying to clarify what I thought the point Dr. Paganini was making. I'm not trying to come to any conclusions. Have I misstated your --

DR. PAGANINI: No, I think you stated correctly what I wanted to do. I'm very concerned that if we take all of the data that has been presented and has been shown and has been published, that there are some very significant responders in that population that carry the mean of those studies. And if we say that there is no indication that carnitine does any good to anybody based on those studies which are very weak, we are

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going to eliminate a significant number, albeit not a large proportion, but still a significant number of folks that do respond to this therapy and have had dramatic responses not only to the delivery of therapy but also to the removal of therapy, and then the redelivery of therapy. We saw in cardiac dysfunction for example, again, in unpublished data. So I don't want to restrict this so that nobody gets it.

On the other side of the coin, I cannot see us approving on the face of the literature here for everyone, and then deciding who improves and who doesn't, and we just put everybody on for three months or six months, and whoever got better are those who had carnitine deficiency, and whoever didn't didn't, because it's going to be a smaller portion of those people that got better, and a larger portion that we're wasting drug and potentially giving them potential for side effects, whether it's oral or IV or whatever. No side effects, it's fine, until you get into large population studies.

So, I don't want to eliminate the drug, I want it to be covered, I want it to be given to patients that would benefit from it. In that

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literature, buried in there, has to be those folks that dramatically improved because of the drug. Define that subgroup and then approve it for that subgroup of people, that's what I'm saying. Now based on this literature, you can't say carnitine works, because it was diluted, but there were people who it really worked in. Why not give them drug, the benefit of that drug, even though they're -- you talked about orphan studies, this is even an orphan within an orphan, and that's a problem with it.

MR. JOHNSON: I agree with what Dr. Paganini is saying. How can we get a motion before you that will allow you to approve the drug once the appropriate people are identified that it would benefit?

DR. HOLOHAN: Kathy?

DR. HELZLSOUER: The best I can tell right now from looking at this is this is a diagnosis of exclusion. You look for everything else that can be correctable and then you're left with patients who have low levels and some symptoms, and you try it, and that's essentially what looking at the Georgia policy seems to have tried to describe, that you look for in these

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conditions, every other possible correctable cause and when those are exhausted, you try carnitine. I don't know, that may be the best we can do at this point, and it seems looking at this, it seems to be very reasonably written, and I think it's trying to put into place to make sure that those other correctable causes are looked for and corrected when possible.

DR. TUNIS: It sounds like though, I think Dr. Paganini's point, with which folks seem to generally be agreeing, is that you could turn that into a motion that says something like, we believe that there is adequate evidence that supplementation with carnitine improves outcomes in some albeit undefined population of patients with ESRD on dialysis. That's something that you could make in the form of a motion that people could vote on. That is obviously not as specific as we'd like, but it says I think what you just said, which is I believe, in totality there is adequate evidence to say this stuff helps some people in some circumstances. So I think at some point there needs to be a motion of that nature.

You may decline to make any motions on any specifics, that's fine. But do you see, you

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were saying you believe there is adequate evidence that convinced you of something, and I'm just trying to get you to say, make in the form of a motion what it convinced you of.

DR. PAGANINI: I will propose this, then. That there seems to be adequate evidence that certain subgroups of patients benefit from carnitine supplement, certain subgroups of end stage renal disease patients on dialysis seem to benefit from carnitine supplement.

DR. JORDAN: I think what Dr. Tunis was trying to say, with the addition of what Kathy talked about, which was clear I think from all the testimony and the literature that we saw, that

when patients have not responded to some of these symptoms that may be a part of that subgroup that we're trying to get at, when they haven't responded to conditional mechanisms, a trial on carnitine and if it works, makes sense. So, you know, would that help clarify the motion that you were trying to get us to make, Dr. Tunis, that we would suggest approval of carnitine use in patients who have not responded to traditional therapies in the conditions in question, or the categories in question, if they haven't responded

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to traditional therapy?

DR. HOLOHAN: Would you pose that proposal in the context of establishment of the kind of guidelines that Dr. Helzlsouer was talking about, rather than just say try everything, because everything depends on the definition of the person who is --

DR. JORDAN: Well, I think clearly according to, you know, reasonable clinical algorithms that have been demonstrated and proposed by people, that there ought to be a way to establish those, as Georgia had done.

DR. HOLOHAN: So let me see if I can recraft what everybody seems to be circling around. That it seems reasonable for Medicare not only to develop a mechanism to define as precisely as possible exactly what is carnitine deficiency, but to also develop a set of rational guidelines for selection of those patients who may prove to be the subset that would benefit, and the only reference I heard to any existing guidelines are those developed by the carrier in Georgia, which you seem to feel was reasonable.

I'm not arguing that that's the sine qua non, but for Medicare to develop a

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process to arrive at a set of reasonable guidelines for the selection of those patients who would be expected to be in the subgroup that would

benefit. Somebody want to --
DR. TUNIS: So maybe, that sounds like you could add that to the --
DR. HOLOHAN: I can't make the motion, somebody else has to.
DR. TUNIS: So maybe just to read back the motion that Dr. Paganini made, which then sounds like somebody wants to amend. You wrote that down, right.
MS. LONG: That there seems to be adequate evidence that certain subgroups of ESRD patients --
DR. HOLOHAN: Benefit from the administration of carnitine supplementation.
DR. TUNIS: Emil, do you want to try to reexpress it? I think your motion was something like, there is adequate evidence that a subgroup of patients with ESRD on hemodialysis will benefit from carnitine supplementation.
DR. PAGANINI: The administration of carnitine supplementation.
DR. TUNIS: There is adequate evidence

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that a subgroup of patients with ESRD on hemodialysis will benefit from administration of carnitine supplementation. And then if somebody wants to reform or add to that an amendment that would add something to do with development of guidelines, and list the rest of this conversation.
MR. JOHNSON: And upon establishment of rational guidelines that identify this patient population, that Medicare coverage be provided.
DR. TUNIS: Okay. And upon establishment of rational guidelines for administration?
MR. JOHNSON: That identify this patient population, that Medicare coverage be provided.
COMMISSIONER GRANT: Should we include that we should take this on back to the Georgia guidelines or is that understood?

DR. TUNIS: It's understood that we will go and look in all the appropriate places, yes.

DR. HELZLSOUER: I second the motion, as amended.

DR. PAGANINI: And I do accept the

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amended language.

MS. LONG: The motion is that there is adequate evidence that certain subgroups of ESRD patients on hemodialysis will benefit from the administration of carnitine supplementation and upon establishment rational guidelines that identify this patient population.

DR. JORDAN: And that Medicare coverage be provided.

DR. TUNIS: We don't actually vote on the Medicare coverage part, we just vote on the adequacy of evidence, so let's just leave that part off.

MS. LONG: All those in favor. It is unanimous.

DR. TUNIS: And you know, I think we're close to finishing up. I think we do have to address the question number two, somewhat in the form of a motion, which is the issue of the route of administration, whether there's adequate evidence that supports one route of administration over another and if so, which route of administration, and with that I'll leave it to you all.

DR. HOLOHAN: Well, let me offer my

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opinion, that I think with the evidence available, considering the first two motions, we can't come close to answering this question. I thought that most of the published data didn't clearly separate the benefit or lack thereof of oral and IV. We've heard allegations about toxic metabolites of the oral form, we have seen no published evidence indicating that that is in fact the case. I will

leave it to you to debate, but I'm not sure that we can come close to addressing this.

DR. METZGER: I would confirm that. I would just point us to the K/DOQI guidelines and where they became most specific, where they were most conclusive, with the EPO resistant anemia, and that subgroup that recommended a four-month trial said PO or IV. They didn't even distinguish in their most specific recommendations.

COMMISSIONER GRANT: I agree that there is insufficient evidence to make any kind of conclusion with that.

MR. JOHNSON: I agree also with that.

DR. JORDAN: The only problem with that is if that's used because it's available PO, that's a reason for a noncoverage decision, I'm not sure that's very acceptable.

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DR. HELZLSOUER: Then I think they have to come up with some evidence one way or the other. I agree that there's -- I mean, you hear about toxicity, but both have been said to be safe and there is no evidence one way or the other. I mean, the question is, is there adequate evidence, and I don't think there is right now with what's been presented to argue one way or the other. It may be that intravenous is better.

DR. JORDAN: So you have the company that is submitting a request for it to be a warning placed on the label, which is a safety issue. When a company makes a safety qualification to a product, it's very unlikely not to be approved, or not to be denied, have FDA say oh, we think it's safe anyway, despite the fact that you're recommending it isn't.

DR. HOLOHAN: But we don't know what the FDA will do.

DR. HELZLSOUER: Right.

DR. HOLOHAN: That was my point.

COMMISSIONER GRANT: But I do want to make sure as far as the quality of the evidence, we were sent a submission in these deliberations

and how are we supposed to treat, what weight do

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we give a representation from the company, a company on its own product, which does address at some length the pros and cons of oral versus IV? Without going into the merits, just does this or does this not have weight as evidence to CMS?

DR. TUNIS: It has weight and it really is left to you all to judge the weight of that versus the weight of the published evidence versus whatever other evidence, but it's not to be ignored, and it sort of has to be judged on its own merits.

DR. HOLOHAN: One of the things I should point out, I don't know how familiar most of the panelists are with the recommendations for evaluating effectiveness from the Executive Committee. It talks about in Section C, when the evidence is insufficient, which sounds like where we are right now, definitive studies are possible but have not been performed, and indicates the reasons why those studies may not have been performed, the newness of the technology, the cost of performing the studies is very high, studies have been performed but are not definitive, that the panel could form a judgment about promising studies and suggest that the technology might be

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considered by HCFA as coverable only in the context of an approved study.

So the panel could conclude that definitive studies are possible but haven't been performed, which is kind of what I thought Dr. Helzlsouer was getting at, and provide a formal encouragement for such studies to be conducted.

DR. PAGANINI: That's for the IV versus oral; is that right?

DR. HOLOHAN: Yes.

DR. PAGANINI: We have heard evidence here that two IRBs refused to allow oral drug to

be given, and I mean, that's pretty heavy evidence that oral probably shouldn't. We have also seen evidence from company that oral should not be given to ESRD patients, or suggested. That's fairly strong evidence from two areas.

Now what I would think is that if we come out with an approval for carnitine in certain subgroups of patients, as we did in the first group, and the group of administration is vague and clouded at the current time, that the best decision we could make is no decision at all.

A fallback position would in fact be

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that we need more information on IV versus oral and perhaps definitive studies should be done, or some definitive documentation should be adhered to. Now if that means that the FDA then slaps something on this drug and says ESRD shouldn't get oral, or that IRBs through the country say no, I think there's enough that I don't want to deal with it, then I think we're sort of pushed into IV as the only method to give the ESRD patient. But I don't think there's any evidence to that right now on either side, so right now the evidence is not one way or the other.

DR. HOLOHAN: Right, I would agree with you. To be a devil's advocate, I should clarify, that we heard testimony that IRBs had refused a suggested protocol, we haven't seen any evidence of that and we don't know why the IRBs -- the IRB was refuse to do it for many reasons that don't necessarily relate to oral toxicity, and I don't think we know that.

DR. METZGER: I have a question. Is there any precedent, I don't know, for the FDA refusing to issue a warning or a recall from a company who is marketing both products and who obviously, their interest is having an IV form the

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only remaining approved form? Has the FDA ever said we're not convinced and we're not going to

stop that kind of labeling when the company itself said we want you to do that?

DR. JORDAN: I seriously doubt it. Do you know, Cathleen?

MS. DOOLEY: I don't know, but I also think you would have to weigh the fact that if the company is voluntarily coming forward with some type of warning when they have used it oral, I think you have to respect that they're coming forward on that and not necessarily they are just doing that to have an IV coverage.

DR. METZGER: Well, I guess my question is, would they have to produce evidence that there is this toxicity, or only theoretical concerns?

MS. DOOLEY: I don't know the answer to that.

DR. HOLOHAN: I think probably the FDA would have to answer that.

DR. JORDAN: I think it comes down to, on this question, whether you're trying to approach it from the negative or the positive. If you're trying to look at, you know, IV versus oral is effective, then it's hard and the evidence is

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mixed. When you're talking about the negative, though, and the safety issue, I think we've seen evidence and actually the more we talk about it, I think it's adequate evidence that there is a safety question associated with oral, in a population to me that's already frail, and we have heard over and over again has chronic comorbidity problems that can lead to further problems. I have to say that that's adequate evidence from my point of view if I was one of those people in that population that the oral isn't safe. And should we just modify this question number 2 to say there is adequate evidence that the route of administration, IV, oral, dialysis fluid, is an important factor in the safety of levo-carnitine therapy in patients with ESRD?

DR. HOLOHAN: Well, I would disagree with that, because I don't think we have seen

evidence of lack of safety of the oral preparation, we have heard statements, but there was nothing in the material that I read that I thought was compelling evidence of safety issues with the oral form.

MS. DOOLEY: I think there is also nothing that we saw, we have to balance that with

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the fact that the FDA approval is in IV for ESRD, because I don't think there was evidence to Ron's point, that if you gave a very high dose of oral, that that person with renal failure could excrete it.

DR. HOLOHAN: Well, except that a supplementary NDA is always at the request of the company, not the FDA. It's not like the FDA reviewed the oral and the IV form and said no, only one of these is appropriate. I mean, I presume Sigma Tau could have if they chose gone to the FDA and asked for a supplemental NDA for the oral form in ESRD patients on dialysis, but they chose not to.

DR. JORDAN: Because they probably believed there was a problem with safety.

DR. HOLOHAN: Well, I don't know. I'm simply making the point that labeling changes don't originate with the Food and Drug Administration, except in safety issues.

DR. PAGANINI: I have to agree with the chairman. I don't believe there was evidence presented here that the oral form is egregiously problematic. Indeed, there is evidence that the oral form may be helpful in some subgroups, and I

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think Dr. Metzger showed some of that in his review, as you did in your review of the literature, so I think there are both sides of that currently here, shows evidence of efficacious subgroup improvement with both IV and/or oral in certain circumstances. I don't think the IV/oral issue is clear at all and I would say it would be

better for us not to make a decision one or the other until evidence shows that one or the other is clearly beneficial.

DR. HOLOHAN: Does anyone want to make a motion on the issue of the route of administration of levo-carnitine?

(Inaudible discussion.)

DR. TUNIS: I was just making a suggestion that one proposal is to just vote up or down on question number two, if that's suitable.

COMMISSIONER GRANT: But without belaboring this, you do have a hook. The size of the health effect if you're trying to compare the two, it could be either as effective but with advantages, or as effective and with no advantages. I mean, isn't that what the quality of the evidence, aren't you saying that right now there is no evidence that one is, that oral is

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either less effective or that IV has more advantages? Does that help you to get closer to precisely what the evidence is?

DR. TUNIS: That I think would be a follow-on question. First you'd have to vote on sort of the route question there, which is, is there adequate evidence that the route of administration is an important factor in clinical effectiveness or safety.

DR. HOLOHAN: Because Mr. Jordan may be rushing to catch a plane, he just pointed to his watch, Mr. Sugarman left a written statement that he asked to be read. It's dated today and it says, please let the record reflect the following comments and voting preference of Mitchell Sugarman.

With respect to the literature review, many of the studies were greater than five years old, some were greater than 15 years told, often considered "out of date" when conducting evidence based medicine analyses. The most recent studies, Brass, Kletzmayer, Sloan, showed very little benefit from the use of L-carnitine in the ESRD

patient.
Most of the studies were small, sample

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size less than 40, and possibly underpowered. K/DOQI recognized from the outset that lack of good quality scientific evidence made supplementation with opinion necessary. Such action weakens the claim that K/DOQI's guidelines are "evidence based."

My summary points: Minimal or no change on effects of anemia, and then he cites Brass, Kletzmayer, Semeniuk. Minimal or no change on muscle strength/morphology (Brass, Thomas). Only possible, underlined twice, reduction in arrhythmia. No change in lipid parameters. No data, underlined, comparing IV to oral PO carnitine, only theoretical arguments concerning toxicity from metabolites. Quality of life was the only measure which appeared to improve with carnitine (Brass and Sloan), which might also be bolstered by the emotional and compelling testimonials provided by the guest speakers during the MCAC meeting.

Conclusion/vote: Given the above, until such time as quality clinical studies are done which determine whether treatment of carnitine deficiency associated with hemodialysis by the administration (oral or IV) of carnitine

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result directly in improved health outcomes, HCFA should not cover, and we've been informed that we can't say that. Recommend multicenter study comparing IV to PO carnitine. Recommend large retrospective analysis of ESRD patients receiving carnitine compared to those not receiving carnitine. Recommend patient selection criteria based on these studies once they are done.

DR. TUNIS: All right. In the interest of time, I would request that somebody make a motion related to question number two for just that language, and we will have a vote on it.

DR. HELZLSOUER: I recommend there is insufficient evidence to make a judgment regarding the route of administration and its effectiveness.
DR. TUNIS: Is there a second?
DR. PAGANINI: Second.
DR. TUNIS: Dr. Paganini seconds it. Any more discussion?
MS. LONG: The motion is that there is insufficient evidence to conclude, there is not adequate evidence that the route of administration, intravenous, oral, dialysis fluid, is an important factor in the clinical effectiveness or safety of L-carnitine therapy in

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patients with ESRD on hemodialysis.
DR. TUNIS: Okay. And so voting yes means you're saying that there's insufficient evidence on the route of administration. So all in favor that there is insufficient evidence on the route? Opposed? Abstaining? The motion carries three to one, that the evidence is insufficient.
DR. HOLOHAN: Kimberly, could you quickly restate what the panel concluded, the several motions made, so that everybody before they leave, understands what they told HCFA?
MS. LONG: Sure. The first motion was for HCFA to establish a mechanism to define that such a condition, i.e., carnitine deficiency, exists in ESRD patient population. There was a unanimous vote for that:
Motion number two. There is adequate evidence that certain subgroups of ESRD patients on hemodialysis will benefit from the administration of carnitine supplementation and upon establishment of rational guidelines that define this patient population. Again, that was unanimous for that motion.
And then again, the last motion is that

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there is not adequate evidence that the route of

administration is an important factor in the clinical effectiveness or safety of L-carnitine in patients with ESRD, and that motion was passed with three votes for that and one against.

DR. HOLOHAN: Well, actually the schedule I have says HCFA announces adjourned. Kimberly?

MS. LONG: Because of time, I would just like to conclude today's session, and would someone move that this meeting be adjourned.

MR. JOHNSON: So move.

MS. LONG: Is there a second?

DR. PAGANINI: Second.

MS. LONG: Thank you everyone for your time and participation. The meeting is adjourned.

(Whereupon, the meeting adjourned at 4:20 p.m.)